Pain

A review of acute and chronic pain, pathways, mediators, and drugs used in analgesia

Laurence Hattersley

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Contents

Introduction

The word “pain” is originally a Greek word, which came into English from the Latin word “poena” meaning **punishment** It is said, more of late, that the study of pain, especially our perception of it, is a study of how the brain works. Mind you, it must start with the perception of pain. I wanted to look into our experience of pain, with particular reference to chronic pain and its ‘inherent quality’ of being difficult to shift!

If you look at this in any sort of detail it can become mind bogglingly, eye-wateringly, complicated! Acute inflammation is frequently a causative factor.

Aetiology of inflammation

Table 1 Causes of acute inflammation

Non-infectious factors	**Infectious factors**
Physical: burns, frostbite, physical injury, foreign bodies, trauma, lionizing radiation	Bacteria viruses other microorganisms
Chemical: glucose, fatty acids, toxins, alcohol, chemical irritants (including fluoride, nickel and other trace elements)	
Biological: damaged cells	
Psychological: excitement	

Acute inflammation will result in certain symptoms.

Table 2 Symptoms of acute inflammation

Aulus Cornelius Celsus (30 BC–38 AD), was the first to clearly describe the cardinal signs of the acute inflammatory process	Rubor	**Redness** - vasodilation
	Calor	**Heat** - local increase in temperature due to hyperemia – the vasodilatation
	Tumor / Oedema	**Swelling** – exudation of fluid from the vascular bed
	Dolor	**Pain** - stimulation of nerves/nociceptors and pH lowering
Galen (130–200 AD), added	Functio laesa	**Loss of function** – the local tissues stop doing what they were doing and start doing something else

Let us return to a probable cause of pain – **inflammation**. Here, let us assume that such inflammation has been caused by trauma or infection and further, let us keep it limited to a local area. I am not downgrading or ignoring any other type. It is just one point of reference. This will cause **acute inflammation**

These characteristics of acute inflammation are the result of a combination of vascular changes (mediated by histamine and 5HT, from mast cells) and other cytokines (IL-1, IL-6, TNF-α, from macrophages and dendritic cells) and activate a cellular response.

This is a generalized reaction, **increasing** blood to the area (to bring in immune cells), **restricting** blood from the area (to prevent any spread of infection) and oedema (to **dilute** any potential poisons). Remember here, that the body only knows **something** is going on, but it doesn't know **what**, yet. Essentially, acute inflammation is **not** a single process, it is not binary in nature ("on'' or ''off''), but it can be regulated by many factors in the cell's environment.

Resolution of inflammation is a coordinated and active process aimed at restoration of tissue integrity and function. A cessation of chemokine signalling blocks neutrophil infiltrating and neutrophils undergo apoptosis (programmed cell death), which attract monocytes and macrophages (phages) to induce their clearance. This reprograms macrophages towards a non-inflammatory state, a key event to restore tissue homeostasis. One symptom of this is pain. First, we need to define pain. There have been a few attempts at a definition.

What is pain?

- A feeling?
- A sensation?
- An emotion?

Aristotle devised the concept of the ***5 senses***. Aristotle said, though, that pain was not a sense (as in the 5 senses), he called it "*A passion of the soul*" and "*an emotion*", because it **does** things to you. You could appreciate this through the Greek Pathos = 'incoming effects from'. We experience a response to a stimulus, in this instance, pain. If we see the word in terms of English Grammar, it means 'the power to evict emotion. We watch or listen to something, and it **does** things to us. So, is pain just a sense, or an emotion that 'colours' what we sense? It suggests there are no pain-specific pathways. It is suggested that even with abnormal stimulation, or *excessive* of normal sensory pathways, you can experience pain.

"***Pain is the Psychical adjunct of a protective reflex" This defines pain as only a mental process and suggests a consciousness, therefore any expression of pain suggests a consciousness e.g. do babies experience pain the same way as us?*** (C S Sherrington 1900)

"Pain is a disagreeable sensation with which everyone has experienced and which we are all recognise" (J. Mackenzie 1909)

"Pain is known to us by experience and described by illustration" (T. Lewis 1942)

Pain is defined today as:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.
(International Association for the Study of Pain 1979)

Sherrington first described the existence of pain receptors - *nociceptors* (nocere – Gr. Injure, damage) back in 1906. However, before that, in the 17th century, there was a theory of mirrors.

Descartes, in 1644 (*Traité de Homme*, published 14 years after his death) described how he understood how the nervous system deals with the pain of potential injury. At the time the process of the neurological system was based on mirrors (the neuron wouldn't be described for another 200 hundred years). This suggested that signals passed from the ear and the eye to the pineal gland (as it was right in the middle of the brain), through animal spirits. Thus, different motions in the gland cause various animal spirits. He also argued that external motions, such as touch and sound, reach the endings of the nerves and affect the animal spirits. For example, heat from fire affects a spot on the skin and sets in motion a chain of reactions, with the animal spirits reaching the brain through the central nervous system, and in turn, animal spirits are sent back to the muscles to move the foot away from the fire. He proposed that pain was something perceived by the brain. He put forward his suggestion as seen in *fig 1*.

Figure 1 Descartes theory on pain

So, if you have an injury, or an 'injury producing stimulus', there would be a transmission of events up a sensation pathway. Then there would be '*a reflection'* of this information into the brain. Then a signal would come from the brain to the muscle, to take the person, or part of the person, **away** from the situation that was causing the injury. Descartes called this process a 'reflex', from the concept of 'mirrors and reflection' that was prevalent at the time. The problem with this model was that it was only relevant for acute pain; then it became a 'good pain'. However, the model doesn't work with chronic pain, neuropathic pain, phantom limb pain or trigeminal or peripheral neuralgia.

Pain is ultimately perceived in the brain. Pain is a brain function; it is in the brain this is curious, considering that the brain has no nociceptors, itself does not feel pain. You might say that all the microphones are in the periphery, but the speakers are in the brain. This is especially curious as the brain itself *doesn't feel* pain. Hence the study of pain, both normal and abnormal, is intrinsic to the scientific endeavour to understand the working of the brain.

Descartes also separated the body and soul (the body ‘just’ being a vessel to carry the soul around). The separation of body and soul has been seized upon by the Jesuits and used by orthodox medicine, such that they now separate themselves from the patient and only see them in terms of ‘labs and scans’. But that is the subject of another essay. Experiments have shown that rats need only **one** experience of pain to learn (if it hurts when I go there, or do that, don’t do it), humans, possibly an *entire lifetime*. Based upon Sherrington, nociception is a **protective reflex**. This is where I say that pain is present to tell us something - but what does it what to tell us?

Candace Pert was a pharmacologist. She discovered the opiate receptor in 1974. After that she mapped receptors of different neurotransmitters, particularly neuropeptides (endorphins and the like), around the body.

For any drug to have an effect, it must act via a receptor. This means that any drug we take that acts on a receptor only **mimics** a substance that is already in the body. With regards to molecules of emotion, there are also receptors in the emotional areas of the brain (the **limbic system**). But such receptors to molecules of emotion also exist in the **heart**. They are also in the **sensory** areas (dorsal roots) of the spinal cord, and they are also in your **gut**. They exist in the **brain stem** and certain key regions *before* they reach the **frontal cortex**. It is only in the cerebral cortex where awareness takes place, that is where you realize and ‘blame’ something and find a reason for anything. Orthodox medicine asserts that we feel emotions because chemicals are released. They say this because they put chemicals into the body, and it ‘creates’ feelings. However, it can also be said that we feel the emotion first and the chemical is released because of that. Or maybe they are both manifestations, expressions, of something else. This creates new subjects, like psychoneuroimmunology; how chemicals that have been discovered in ‘separate’ systems are shared and expressed in different systems in the body. But if such an overlap like this does exist, why do we need to create another ‘reductionist’ subject when we can call it ‘biology’? Candace Pert called it **Bodymind**.

What does pain do to us?

Are there different types of pain? Sherrington’s definition of pain only applies to consciousness and, more than that, ‘*good pain’* - the pain that results from injury and alarm. Descartes’ model was also one of ‘good pain’. But what about the pain of *disease*? The sensation of pain is unlike any of the other senses we have. All the other senses (touch, taste, hearing sight and smell) will **habituate**; you get used to them. If you turn the washing machine on, you hear it at first but after a while you don’t hear it anymore.

Pain is different. Pain only **amplifies**. If you are putting up a picture and miss the nail, hitting your thumb with the hammer, it will hurt a lot, and that pain will continue for several days until the inflammatory process from the trauma resolves. This pain is *inflammatory pain*.

Tissue **damage** may be:

- Mechanical
- Thermal
- Chemical
- Electrical
- Metabolic (e.g. hypoxaemia, hypoglycaemia)

There is a third type of pain - **neuropathic pain**. This may begin from nerve damage or even *idiopathic* (no apparent reason). Either way the pain experienced by the person is not commensurate with any stimulus; with trigeminal neuralgia, even a gentle breeze on the skin can cause a sensation like fire. Such constant pain is not a normal, helpful, or protective process. Neuropathic pain is very difficult to treat.

John Bonica (an American anaesthesiologist who pioneered pain clinics) explained the difference between the good protective pain and the awful pathological pain, ***"Whereas acute symptomatic serves the useful purpose of warning, chronic pain is a malefic force which imposes severe emotional, physical, and economic stresses on the patient".***

With that we can remind ourselves of the definition of pain used today: "***Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*** (The International Association of the Study of Pain – 1979)

I ask patients if the pain is constant or intermittent, to which they sometimes say,

- "It's constant - all the time".
- Then I ask, "So, the pain is 24/7? Is there any time you are free of pain?
- "Ah, no. It doesn't hurt when I lie down"

This doesn't mean they were lying; it does suggest, however, that the pain has possibly become their singular point of focus, their **only** reality. Another equally difficult question to answer is what **type** of pain it is. I had one man who, when I asked him that question, he said, "What do you mean what type of pain is it? It **HURTS**"

After (possibly a long time after) Sherrington gave us the term **nociception**, introducing the principle that there are structures or receptors that are there to feel pain; the hunt was on to find them. This is not as easy as it sounds. It could be said that to feel pain, there must be a **sensor** for the pain. It is like that old conundrum: if a tree falls in the forest and there is no one there to hear it, did it make a noise? In truth, we humans have a very limited perception of the outside world. In fact, there is a lot more in the outside world than we can see, hear and touch. Our hearing detects vibration in the air of between 20 - 20,000Hz (I can't hear anywhere near 20,000Hz anymore). But we can only hear the noise if we have functioning hearing (via air conduction - e.g. the comedian and writer Eric Sykes had poor air conduction, so

had glasses that allowed him to hear via bone conduction). Spike Milligan wrote a book called The Looney, about a man called Mick Looney. He got up in the morning and smelled fried eggs. He went downstairs with great anticipation, but what he got wasn't fried eggs. The problem was that the smell of fried eggs was the only thing he could smell, no matter what the smell was.

Effects of pain may be more serious for older people:

- Chronic pain can make them less able to function and more dependent on other people.
- They may lose sleep and still feel exhausted.
- They may lose their appetite, resulting in undernutrition.
- Pain may prevent people from interacting with others and from going out. As a result, they can become isolated and depressed.
- Pain can make people less active. Lack of activity can lead to loss of muscle strength and flexibility, making activity even more difficult and increasing the risk of falls.

How do we feel pain?

But all that the receptor does is detect such sensation for what it is designed. The thing that makes sense of all our senses is the **brain**. But the information of the sensation has to get there. For us to feel anything, we need **receptors**.

Noxious stimuli are stimuli that elicit tissue damage and activate **nociceptors.**

Nociceptors are sensory receptors that detect signals from damaged tissue or the threat of damage and indirectly also respond to chemicals released from the damaged tissue. Nociceptors are not uniformly sensitive. They fall into several categories, depending on their responses to mechanical, thermal, and/or chemical stimulation liberated by the damage, tumour, and/or inflammation. Not all the tissues share the same wealth of receptors (with us, particularly pain). All the solid organs (brain, lungs, liver) **do not** have pain receptors, but all the hollow ones (e.g. tubes, gut, and ureter) are **richly** innervated - ask anyone who has had to pass a kidney stone.

The gut has no pain receptors that detect heat (yes, you can burn the inner lining of the gut, though do not to be confused with chemical, like acid or chili), but do have them for other stimuli. Pain receptors in the abdomen respond to mechanical and chemical stimuli. **Stretch** is the principal mechanical stimulus involved in visceral nociception, although distention, contraction, traction, compression, and torsion are also perceived. Visceral receptors responsible for these sensations are located on serosal surfaces, within the mesentery, and within the walls of hollow viscera. Visceral mucosal receptors respond primarily to chemical stimuli, while other visceral nociceptors respond to chemical or mechanical stimuli. These reflexes going from the viscera to the spine can express themselves in the physical (somatic) body and

are called viscerosomatic reflexes. Of course, this reflex principle can work both ways, the other being somatovisceral reflexes. Skin has no receptors for **ultraviolet radiation**. UV rays cause inflammation in skin (sunburn) so it is the **inflammation** that is the cause of the pain we feel. Not only do these stimulate the nociceptors **directly**, but they also change their **threshold**, making them fire more readily (*hyperalgesia*) - so we feel pain in sunburned skin even the lightest touch (*allodynia*). There is a benefit of this - we stay away from it while it heals.

Cognitive pain (pain of which we are aware)

Our experience of pain has three components. We define them individually, but they cannot be seen separately from each other. They are:

- **Sensory**
- **Emotional**
- **Cognitive**

The sensory component is responsible for the recognition of pain, nociception of any harmful or potentially harmful stimulus. It is the ‘Ouch’ component. Its origin is in the peripheral system in the skin, joints, muscles and internal organs. The information of these receptors finds their way into the sensory regions of the brain, as espoused above, where they are resolved into the sensory experience of pain. It might be said that this stage is similar to any other sensation. The emotional element is our **affective reaction** to it. Normally this is an aversive and unpleasant emotional response. It makes us unhappy and triggers aversive reactions. It can make us cry, change our breathing and heart rate and affect the regulation of our internal organs (through the autonomic nervous system).

The heart of the **emotional** element is an aversion and ‘**get rid of my pain’**.

Table 3 Types of receptor

Type of receptor	**Stimulus**
Mechanoreceptors	Respond to mechanical stimuli: stroking, stretching, or vibration of the skin
Thermoreceptors	Respond to cold or hot temperatures
Chemoreceptors Including smell and taste	Respond to certain types of chemicals either applied externally or released within the skin, such as histamine from an inflammation

Regarding the mechanoreceptors, specifically, there are:

Name	**Location**	**Function**
Meissner’s corpuscles	Dermal papilla of hairless skin on the fingers, toes, palms, soles, lips, eyelids, nipples, and genital organs.	Highest sensitivity. Detects light touch in non-hairy skin (palms and soles)

Pacinian corpuscle	Skin and other internal organs	Low-threshold mechanoreceptor responsive to vibration or pressure
Merkel's disks	Basal epidermis in glabrous and hairy skin, around the apical ends of some hair follicles	Light touch and sustained pressure, and are sensitive to edges of objects
Ruffini corpuscles	Cutaneous tissue between the dermal papillae and the hypodermis. Highest density around the fingernail	Sensitive to skin stretch, and contributes to the kinesthetic sense of and control of finger position and movement

Table 4 Types and sites of mechanoreceptors

The experience of **pain** usually starts with activation of *nociceptors*—receptors that fire **specifically** to potentially tissue-damaging stimuli. Most of the nociceptors are subtypes of either chemoreceptors or mechanoreceptors. When tissue is damaged or inflamed, certain chemical substances are released from the cells, and these substances activate the chemosensitive nociceptors. Mechanoreceptive nociceptors have a high threshold for activation—they respond to mechanical stimulation that is so intense it might damage the tissue.

Nociceptors are not uniformly sensitive. They fall into several categories, depending on their responses to mechanical, thermal, and/or chemical stimulation liberated by the damage, tumour, and/or inflammation.

Skin nociceptors may be divided into four categories based on function.

Table 5 Types of nociceptors

Type of receptor	Stimulation
Mechanonociceptor	Only to intense mechanical stimulation such as pinching, cutting or stretching.
Thermal nociceptors	Respond to the above stimuli as well as to thermal stimuli
Chemical nociceptors	Respond only to chemical substances
Polymodal nociceptors	Respond to high intensity stimuli such as mechanical, thermal and to chemical substances like the previous three types.

A characteristic feature of nociceptors is their tendency to be **sensitized** by prolonged stimulation, making them respond to other sensations as well.

Joint Nociceptors. The joint capsules and ligaments contain high-threshold ***mechanoreceptors***, ***polymodal nociceptors***, and ***"silent" nociceptors***. These silent receptors are normally unresponsive to noxious mechanical stimulation but become "*awakened*" (responsive) to mechanical stimulation during *inflammation* and after tissue injury. One possible explanation of the "awakening" phenomenon is that *continuous stimulation* from the damaged tissue **reduces the threshold** of these

nociceptors and causes them to begin to respond. This activation of silent nociceptors may contribute to the induction of **hyperalgesia**, central sensitization, and **allodynia**. Many visceral nociceptors are silent nociceptors.

> Many of the fibres innervating these endings in the joint capsule contain **neuropeptides**, such as substance P (SP) and calcitonin gene-related peptide (CGRP). Liberation of such peptides is believed to play a role in the development of inflammatory arthritis (more on that later)

Tissue damage

These mediators, including

When tissue damage occurs, chemicals like inflammatory mediators from mast cells and dendritic cells (ATP), bradykinin, glutamate, histamine, interleukin 1 and 6 (IL-1, IL-6), Serotonin (5HT – 5-hydroxytryptamine), platelet-activating factor, nerve growth factor, prostaglandin, and tumor necrosis factor-α (TNF-α), are released from an injury site or the nerve endings themselves, serve to sensitize nociceptors, thereby amplifying pain perception. This leads to the initiation of an action potential at the initial segment of the axon.

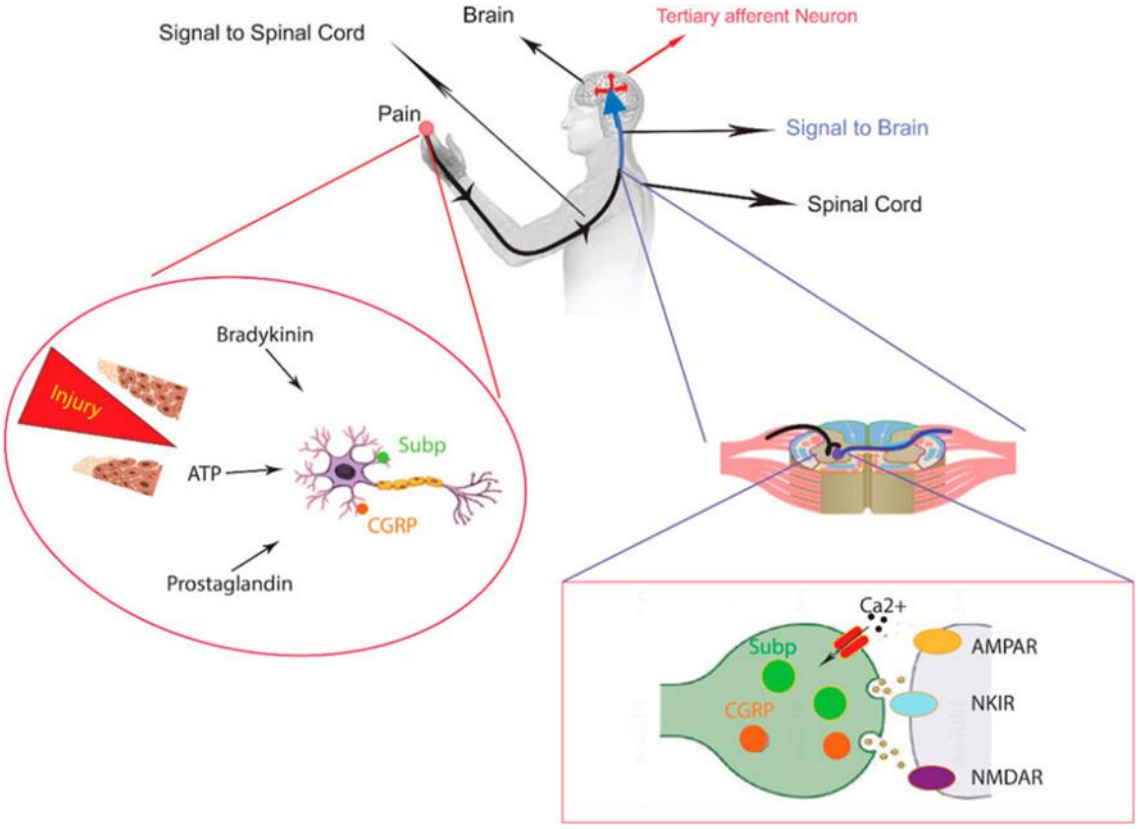


Figure 2 Tissue damage in acute inflammation

Visceral Nociceptors. Visceral organs contain mechanical pressure, temperature, chemical and silent nociceptors. The visceral nociceptors are scattered, with several millimeters between them, and in some organs, there are several centimeters

between each nociceptor. Many of the visceral nociceptors are silent. Noxious information from visceral organs and skin are carried to the CNS in different pathways.

As you will recall from your physiology, there are different types of nerves with respect to their diameter and the myelination of the nerve fibre. Generally:

Thicker (greater diameter) fibres are faster (in terms of speed of impulses)

Myelinated fibres are faster

Now, we must talk about the nerve fibres that carry all this information **to** the spinal cord. You might recall from your physiology that the *motor* nerves have **two orders**, in that there is a '*first order'* (upper motor neuron) nerve takes information from the motor cortex down to the ventral horn of the spinal cord. Then a '*second order'* (lower motor neuron) neuron takes that information of the spinal cord to the muscle or gland, that is its target tissue in the body.

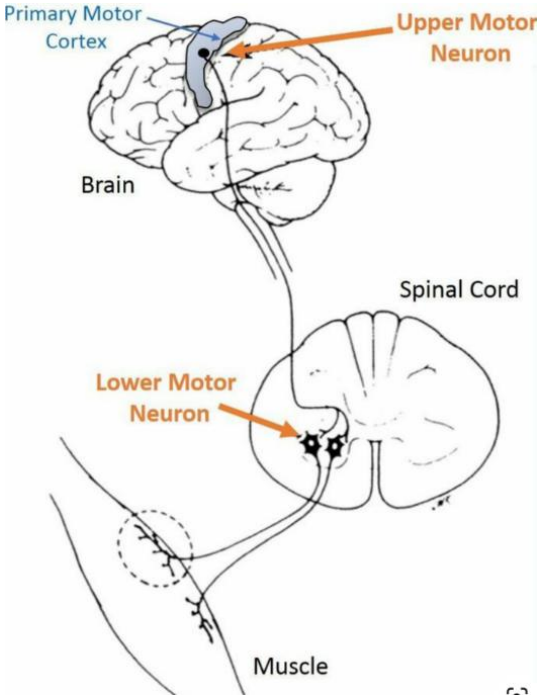


Figure 3 Motor neurons

In the *sensory* system there are **three orders** of neurons to get the information up to the relevant part of the brain.

Table 6 Orders of sensory neurons

Neuron	From	To
First order	Sensory pain receptor	Dorsal root of spinal cord
Second order	Dorsal root	Thalamus
Third order	Thalamus	Sensory cortex in parietal lobe

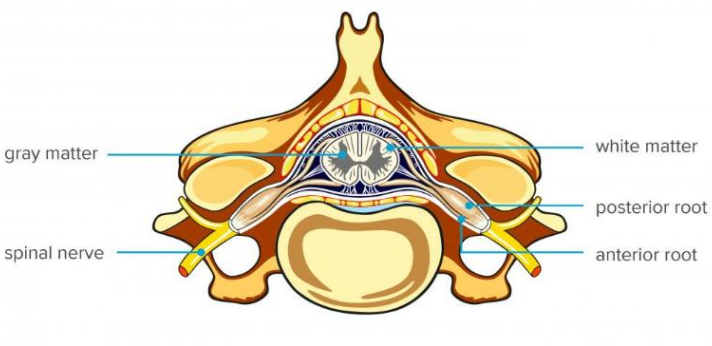


Figure 4 Cross section of vertebra in the neck

Fig 4 shows a typical cross-section of the spine, here in the cervical spine (neck). This shows the vertebra itself, along with the vertebral canal containing the spinal cord. Now, just looking at the spinal cord itself, we see within it a characteristic 'H' pattern:

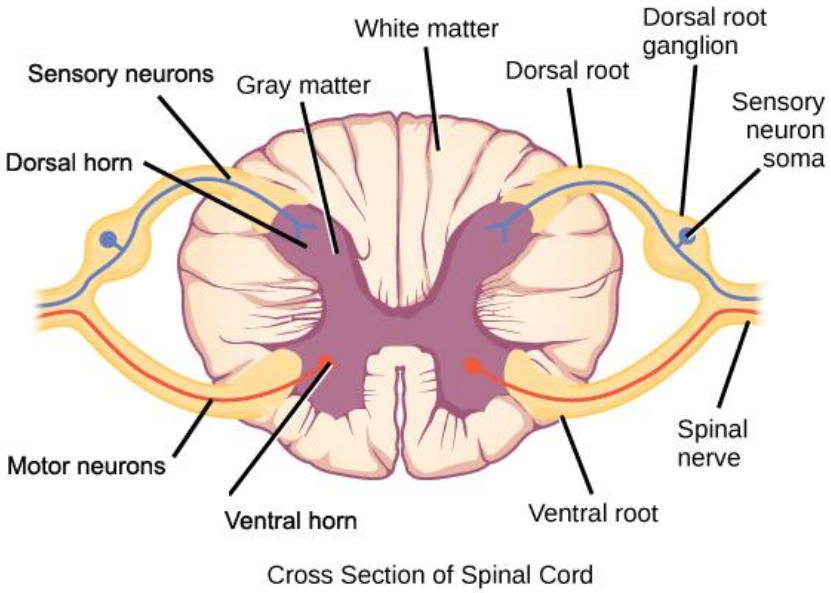


Figure 5 Cross section of spinal cord

In fig 5, everything pale is '**white matter'** (myelinated fibres). Everything darker (the 'H' shape) is **'grey matter'** (non-myelinated fibres and cell nerve cell bodies). Remember that the myelination of fibres increases the speed of the impulses along those fibres (hence the white matter will all be **long tract** fibres passing up and down the spinal cord). Everything towards the back (the top, here) is described as posterior, or dorsal. Everything towards the front (the bottom, here) is anterior, or **ventral.** Hence the grey matter will have **dorsal roots** and **ventral roots**. The 'H' changes a little in shape a bit as it goes down the spinal cord, but the 'H' of the grey matter remains.

All **afferent** nerve fibres (carrying sensory information **from** the tissues, towards the spinal cord) enter the spinal cord via the **dorsal root**.

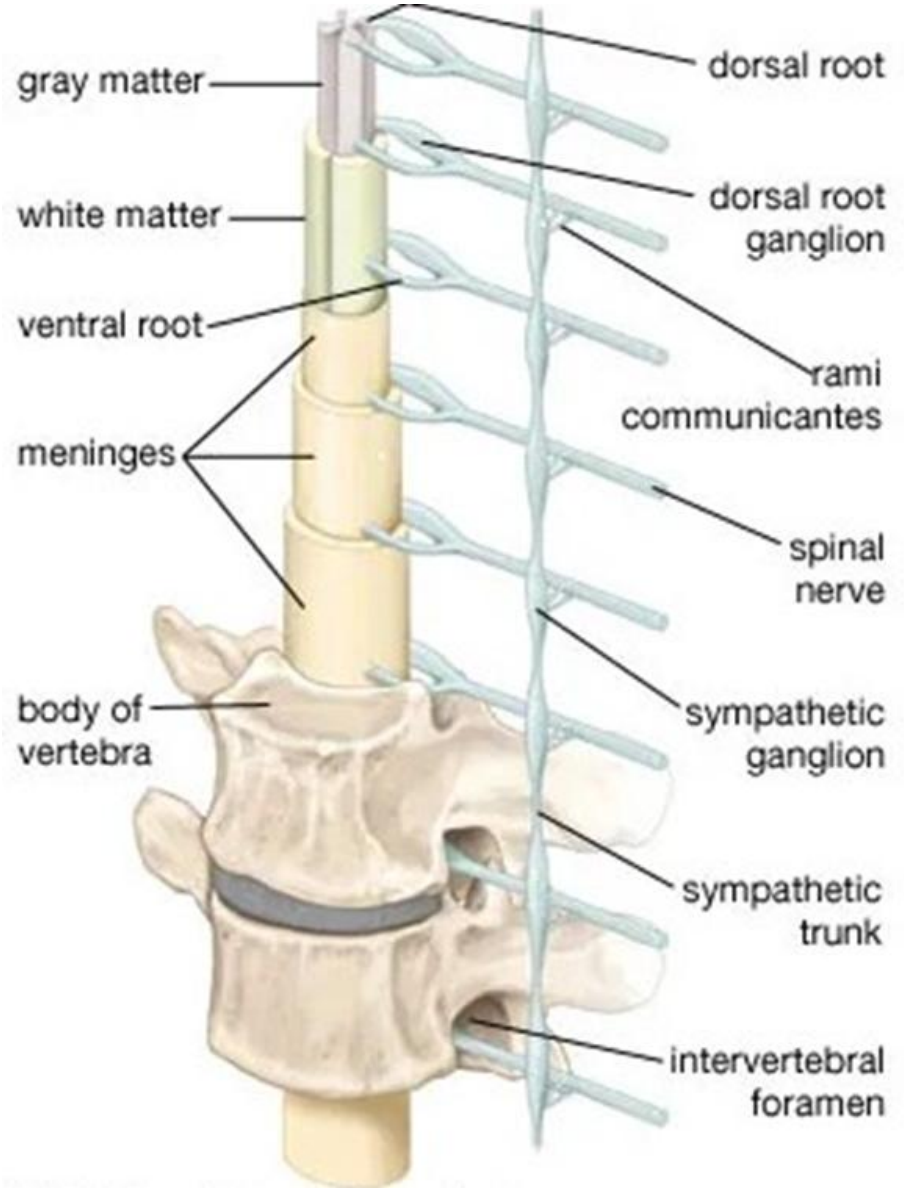


Figure 6 Diagram showing the layers within the spinal cord

Efferent nerve fibres (carrying motor information away from the spinal cord **to** the tissues) emerge via the **ventral root**.
There are different types of afferent nerves (depending upon their diameter and myelination) that carry sensory information from nociceptors

They are Aβ (A-beta), Aδ (A-delta), and C-fibres.

These are known as the **primary afferent** (first order) fibres:

Table 7 Classification of sensory fibres

Type of fibre	Stimulus	Activation threshold	Diameter	Myelination	Speed of impulse
Aα	Muscle spindle fibres	Low (sensitive)	13-20μm	high	80-120ms^{-1}
Aα	Golgi tendon organ	Low (sensitive)	13-20μm	high	80-120ms^{-1}
Aβ	Touch, non-noxious inc. Pacinian corpuscle	Low (sensitive)	Largest 6-12μm	High	30-70ms^{-1}
Aδ	Noxious, rapid, sharp, localized pain, touch, pressure, cold	High and low	Smaller 1-5μm	Some	12-30 ms^{-1}
C	Noxious, dull, not localized pain, itch, sensual touch, warmth, burn, cramp	High (least sensitive)	Thin 0.2-1.5μm	Low	1ms^{-1}

Fast sensory fibres

- Arise from superficial tissues and serosal membranes
- Localized
- Sensation is pricking in nature
- Short duration
- Transmitted by Aδ fibres
- Felt only *during* injury

Slow sensory fibres

- Arise from superficial and deep tissues and urea
- Sensation is burning, dull aching in nature
- Long duration
- Transmitted by C-fibres
- Felt *after* injury (1s)

To say that the sensory fibres enter the dorsal horn is correct but an oversimplification. The dorsal horn of the spinal cord has layers. The sensory fibres must first enter an area called the **Lissauer's tract**.

After entry into the dorsal horn a few of these fibres then pass up or down 1 – 2 segments (layers of spinal cord) before synapsing with the second order neuron in the **substantia gelatinosa** in the tip of the dorsal horn.

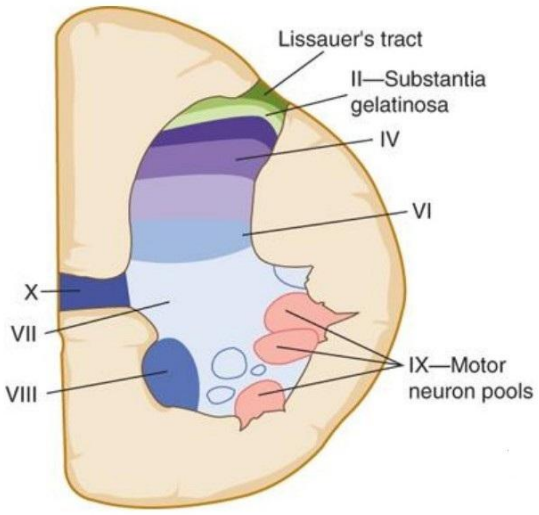


Figure 7 Lissauer's Tract

Second Order Neurons

The Neospinothalamic Tract

The first order neurons synpase with the second order neurons, These carry the sensory information from the **substantia gelatinosa** to the **thalamus**. These second orer fibres **decussate** within the spinal cord to its opposite side. Now, none of the diagrams I have looked at here seem to agree about the *precise route* of this decussation. Most of them show decussation through the grey matter, however, they actually decussate through the **anterior commisure** of the white matter. The anterior or ventral white commissure is a collection of nerve fibres that cross the midline (just anterior to the grey matter in fig 8) of the spinal cord and transmit information from or to the **contralatera**l side of the brain.

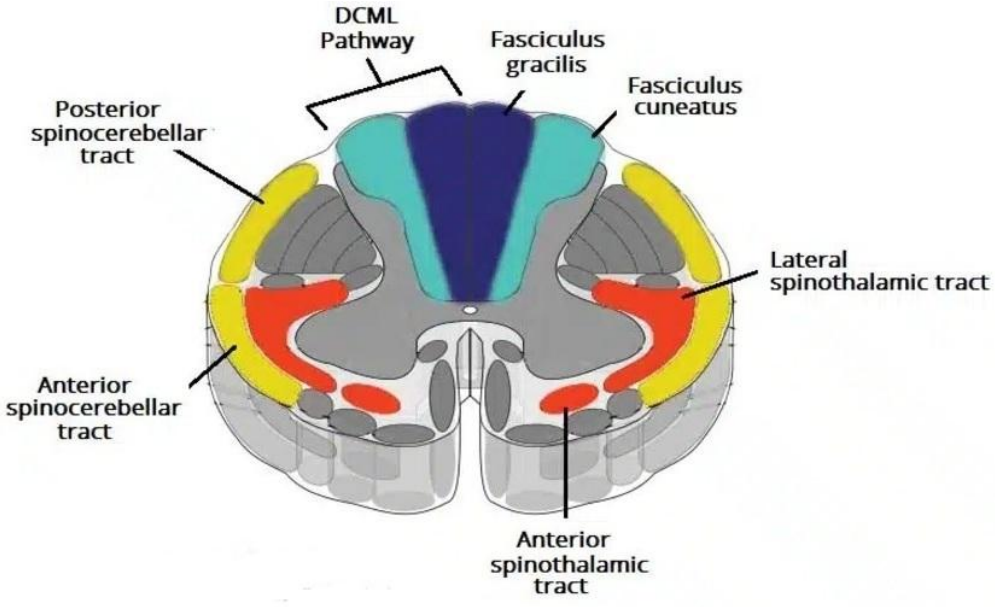


Figure 8 Tracts within the spinal cord

Whichever you route you see, it then form two distinct tracts:

> Crude touch and pressure fibres – enter the **anterior spinothalamic tract** (see fig 8)
>
> Pain and temperature fibres – enter the **lateral spinothalamic tract** (see fig 8)

Although they are functionally distinct, these tracts run alongside each other, and they can be considered as a single pathway. They travel cephald within the spinal cord, synapsing in the **thalamus** (see fig 8). From the **thalamus**, these second order neuron synapse with the **third order neurons**, which then pass to the **post central gyrus** of the *cerebral cortex.* It is here where we consciously **feel** the pain, and that is contained therein.

Here is a link to Candace Pert (a pharmacologist) explaining it: https://drive.google.com/file/d/16Kn59WbE-fqRq2QN27-ZVSrLHaKTvIX2/view?usp=sharing

Now, fig 9 shows all three orders of neurons. I have seen these diagrams and can understand any confusion you have looking at them! The two bulbous pink sub-cortical structures in the brain are the left and right **thalamus**. So, to recap:

- The **first order neuron** – passes from the peripheral receptor to the dorsal horn of the spinla cord, and synpases with the secod order neuron
- The **second order neuron** decussates to the spinothalamic tract and ascends through the **brain stem** and **periaqeductal grey** (more about that in a minute) to the **thalamus**, where it synapses with the third order neuron
- The **third order neuron** then passes to the **post-central gyrus** of the **cerebral cortex**

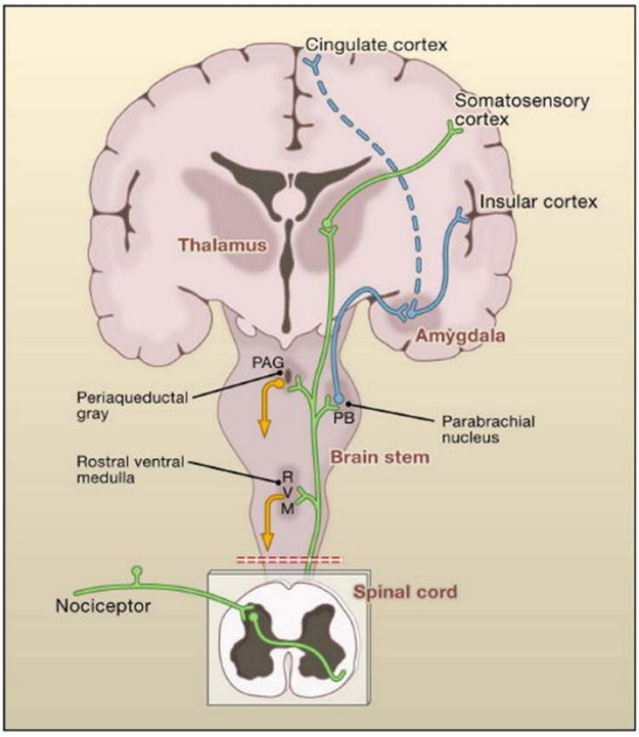


Figure 9 Diagram showing the three orders of sensory neurons

Perception of pain in the head

- From the **head, face** and **intraoral structures** the first-order nociceptive neurons, and these trigeminal fibres enter the **pons**
- They then descend to the **medulla** and make synaptic connections in the **spinal trigeminal nucleus**,
- They then decussate and ascend as **trigeminothalamic tract** (or trigeminal lemniscus)
- The C fibers terminate in the **thalamus**
- This pathway is responsible for the immediate awareness of a painful sensation and for awareness of the exact location of the painful stimulus.

This is shown in Fig 10. Here the solid blue line represents the spinothalamic tract. The broken blue line represents the **spinal trigeminal tract.** Remember what I said about the spinal cord **grey matter** – it is seen as an '**H**' in the middle. Hence on this diagram, the two lower sections are the **spinal cord**. The three layers above that are the **medulla**, the **pons** and the **midbrain** (these, together, formiing the **brain stem**).

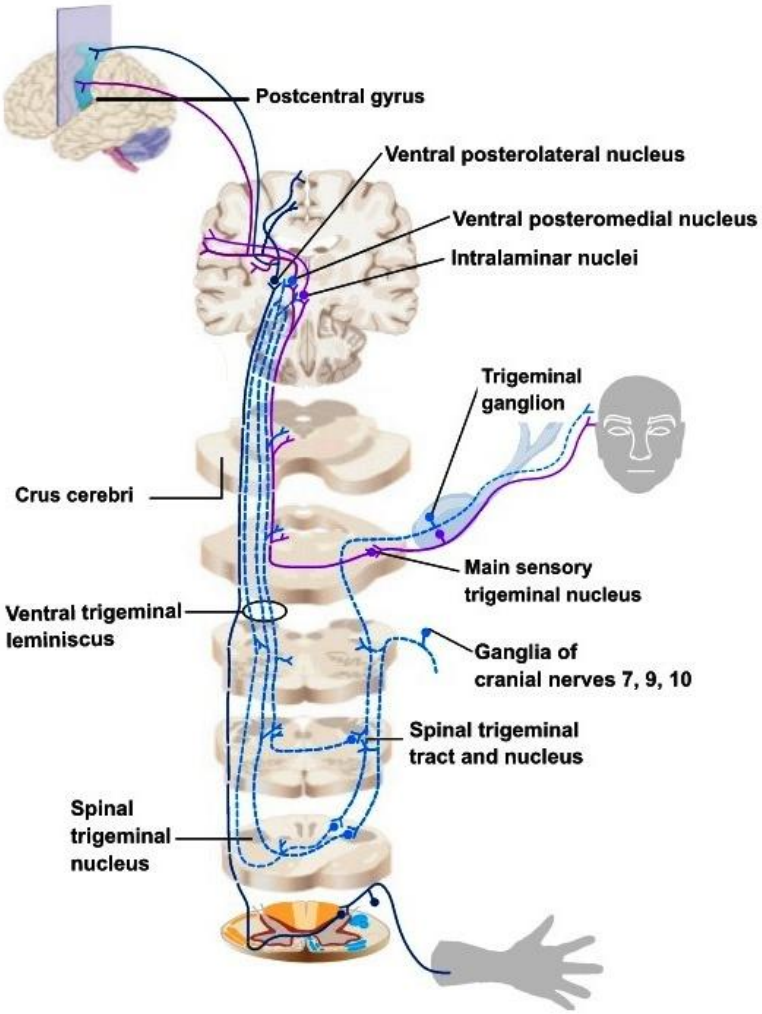


Figure 10 Sensory and spinal trigeminal tracts

Now, all this gives us a broad overview of our sensory pathways from the peripheral to the brain. With this, though, there are ‘older’ nerve tracts.

The Paleospinothalamic tract

- The paleospinothalamic tract (fig 11) is phylogenetically ‘old’. The first-order nociceptive neurons mainly make synaptic connections in **substantia gelatinosa**
- The second-order neurons also receive input from mechanoreceptors and thermoreceptors (those also going to the neospinothalamic tract)
- The nerve cells here have a wide range of nociceptors. Most of their axons decussate and ascend in the spinal cord primarily in the **anterior spinal thalamic** tract (fig 8). These fibres contain several tracts, making synaptic connections in different locations:
- In the **mesencephalic reticular formation** (MFR) and
- The **periaqueductal grey** (PAG) in the brain stem, and they are also called **spinoreticular** tract; in the tectum, and these fibers are known as the **spinotectal** or spinomedullary tract.
- The above three fibre tracts are the **paleospinothalamic tract**. The innervation of these three tracts is **bilateral** because some of the ascending fibres are both **ipsilateral** (on the same side), and **contralateral** (on the opposite side)
- These fibres synapse bilaterally in the post-central cerebral cortex. The paleospinothalamic pathway also activates **brain stem** nuclei which are the origin of **descending pain suppression** pathway regulating noxious input at the spinal cord level. (more later).

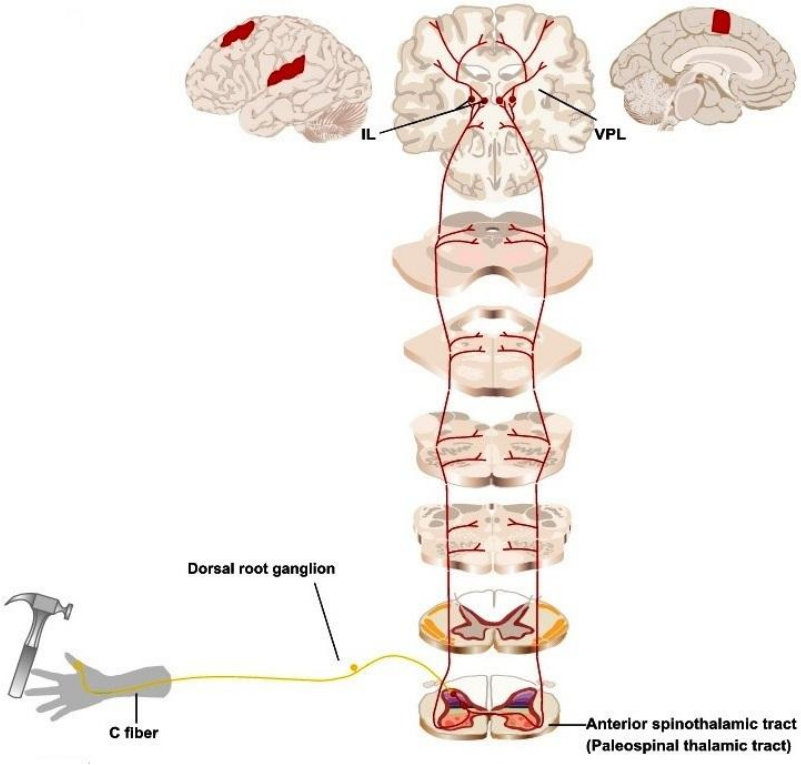


Figure 11 The Paleospinothalamic pathway

The Archispinothalamic Tract

This is possibly tending towards too much detail, but I feel it's worth a mention with regard to the changes pain causes within us regarding **emotions** and **autonomic reflexes** (separate from the viscerosomatic reflexes).

The archispinothalamic tract (fig 12) is a **multisynaptic** diffuse tract (so, possibly the oldest and slowest) that carries noxious information.

- The first-order nociceptive neurons make synaptic connections in the **substantia gelatinosa**. From here, fibres ascend and descend in the spinal cord via the **multisynaptic propriospinal pathway** (fig 12) surrounding the grey matter
- These synapse with cells in the **mid-brain reticular formation** (MRF) and **periaqueductal grey** (PAG) area. Further multisynaptic diffuse pathways ascend to the thalamus and send collaterals to the **hypothalamu**s and to the **limbic** system nuclei.
- These fibres mediate **visceral**, **emotional** and **autonomic** reactions to pain.

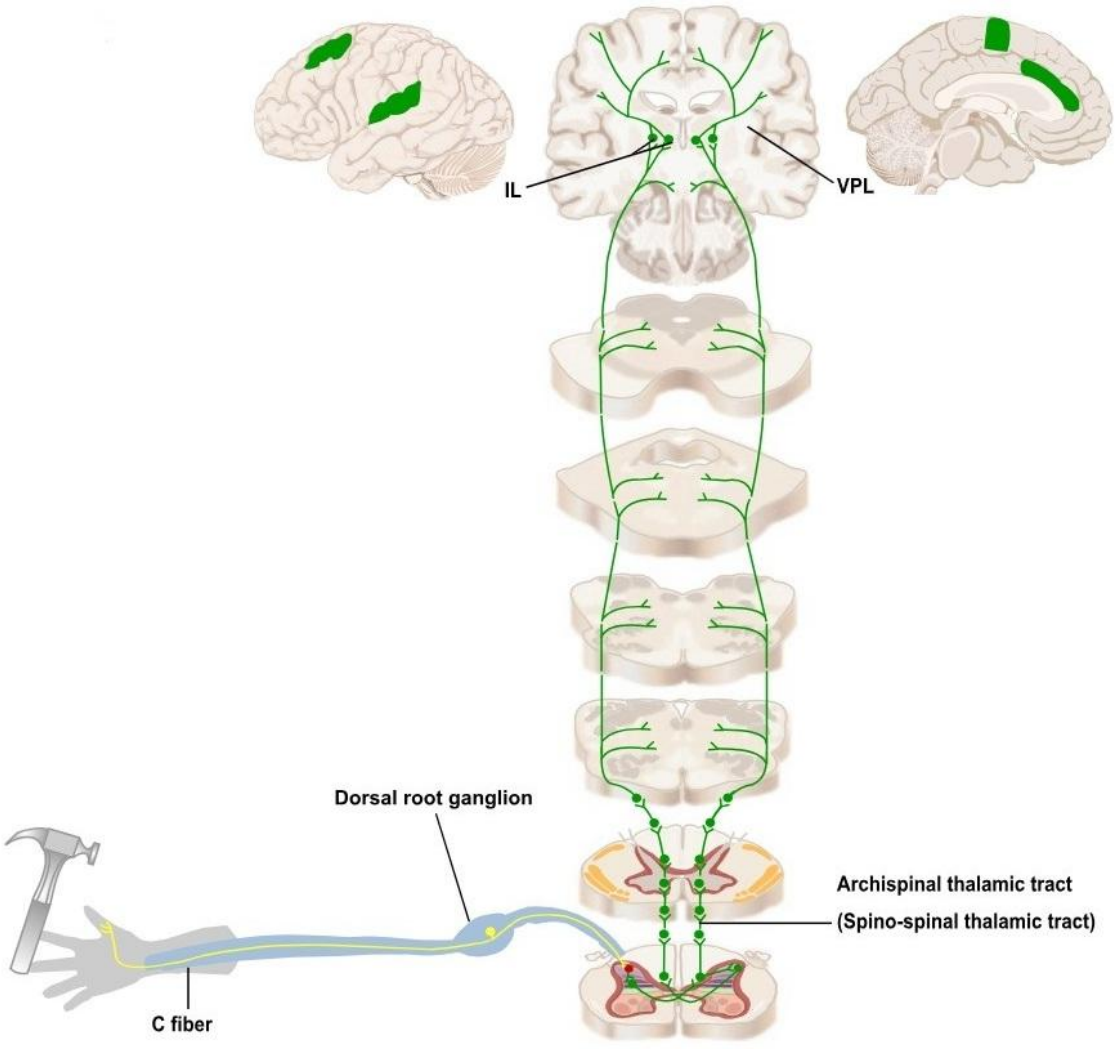


Figure 12 Archispinothalamic tract

Visceral Pain

Although clinically common, the nature of referred pain remains an enigma. In the visceral organs, the free nerve endings are scattered. Nociceptors respond to mechanical stimulation such as pressure, tissue damage, and chemical stimulation. Most noxious information carried by visceral afferents does **not** give rise to conscious sensation. Visceral pain is diffuse, less precisely graded and typically accompanied by slowing of the heart, lowered blood pressure, cold sweats and nausea.

In the visceral organs, any stimulus that excites these nerve endings causes **visceral pain**. Such stimuli include spasm of the **smooth muscle** in a hollow viscus (the **tubes/bags** of the viscera), or distention or stretching of a ligament, such as a stone blocking the ureter or the gall ducts. **Stretching** of the tissues such as intestinal obstruction can also provoke visceral pain. Visceral pain is also caused by chemical means because of **gastrointestinal lesions**, **tumours** as well as **thrombosis** of an artery. In many cases, visceral pain is not localized to the site of its cause, but rather to a distant site.

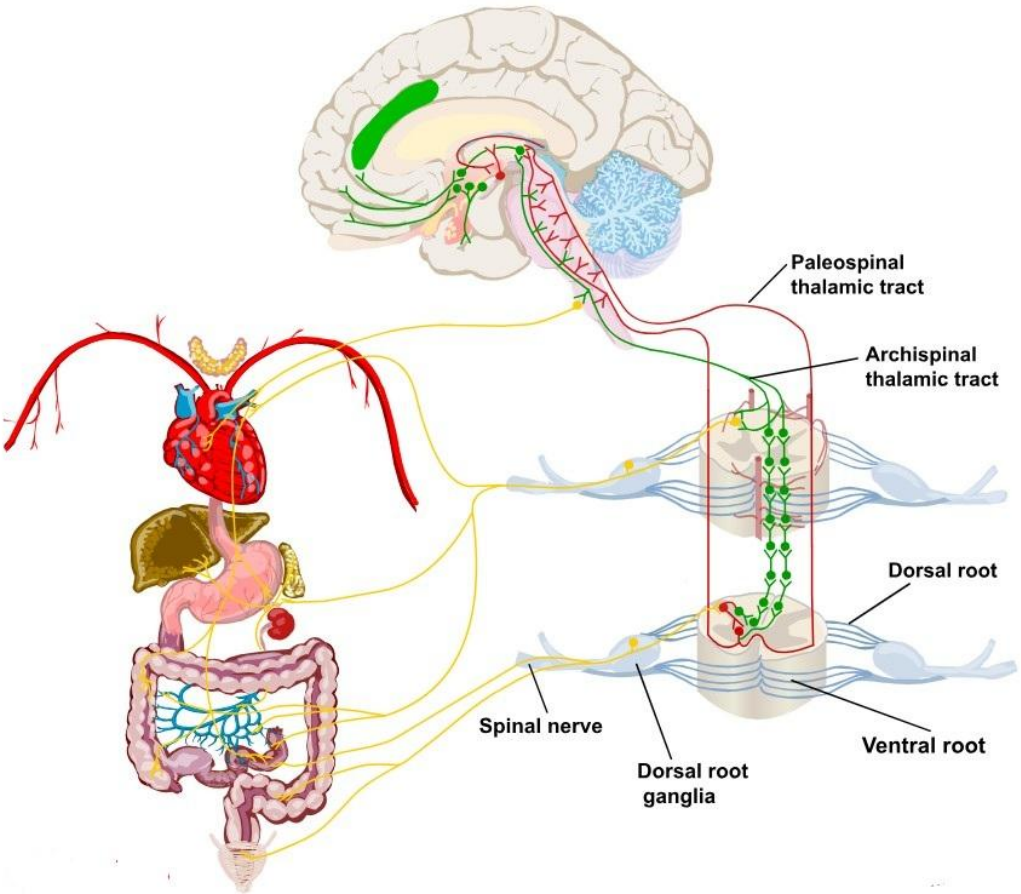


Figure 13 Visceral pain pathways

This can result in **referred pain**

Referred Pain

Referred pain is a painful sensation at a site **other than** the injured one. The pain is not localized to the site of its cause (visceral organ) but instead is experienced at a distant site. Sensory fibres from viscera enter the spinal cord, then go up or down several segments before emerging. Effectively pain can be experienced in the physical body in areas that share that **same spinal segment as of the sensory input**. It can also be via **embryological origins** of those viscera and their attachments.

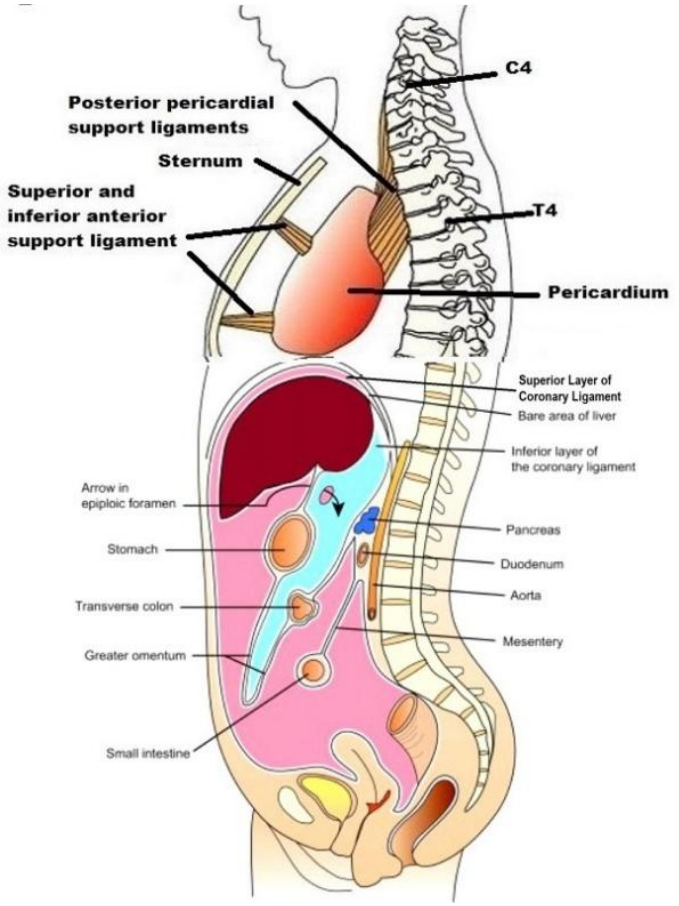


Figure 14 Section through the body showing attachments of viscera

Here, we can just focus on the heart. You can see that it sits on top of the respiratory diaphragm. It also has attachments to the sternum as well as the cervical and upper thoracic spine. These relationships can explain the referred symptoms of cardiac symptoms: retrosternal pain, symptoms that can be interpreted as ‘heartburn/upset stomach’, as well as pain between the shoulder blades.

All that without the referred symptoms via the nervous system.

The neurological convergence gives rise to referred pain. For example, as the heart and liver have their embryological origins in the cervical region, the symptoms will refer back to those areas, here the neck and shoulders. Pain resulting from distention of the colon is referred to the periumbilical area. The following are some hypotheses to explain referred pain:

Common dermatome hypothesis. When pain is referred, it is usually to a structure that developed from the same embryonic segment or dermatome as the structure in which the pain originates. Radiating pain down the left arm is the result of a myocardial infarction, or pain originating from the shoulder (**dermatomes C3-5**) (fig 16).

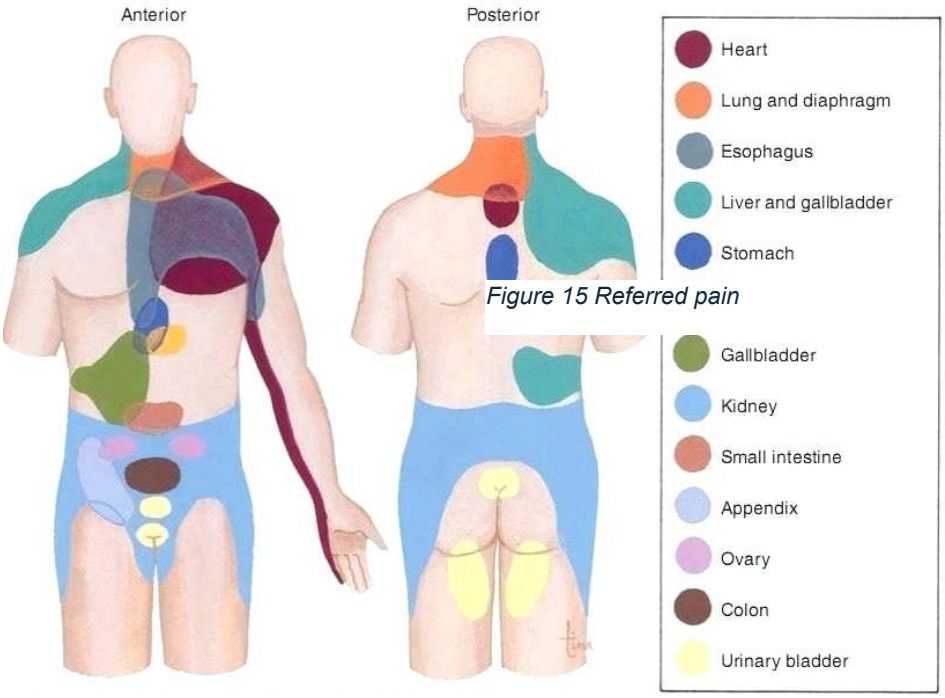


Figure 15 Referred pain

Figure 16 Convergence in referred pain is carried via the paleospinothalamic tract

Convergence and facilitation theories. Inputs from visceral and skin receptors converge on the same spinal cord neuron (i.e. viscerosomatic neurons). Therefore, visceral pain is referred to skin area because the nociceptors' terminals from the viscera terminate in the spinal cord on the same neurons that receive input from the skin. (Fig 17)

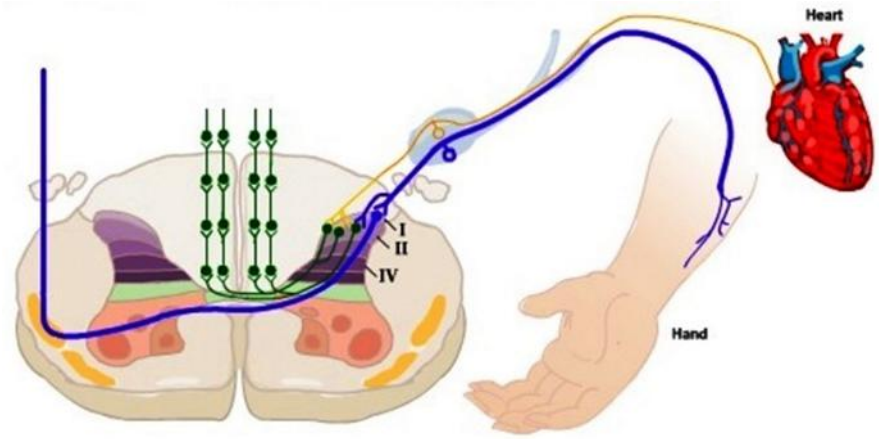


Figure 17 Convergent referred pain via archispinothalamic tract

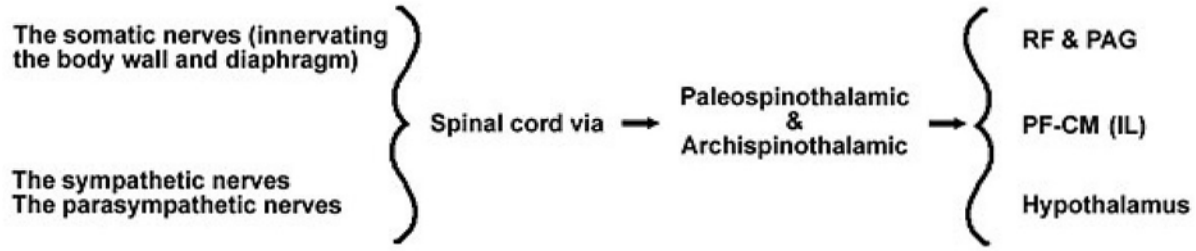


Figure 18 Pathways of pain to brain

Facilitation or irritable focus. Pain impulses from the viscera alone are unable to pass directly from spinal cord neurons to the brain but create an "irritable focus". When visceral and skin impulses arrive together, the information transmitted to higher centers and the brain **interprets that pain** as being from the skin

Another example of visceral pain is the pain from a herniated or **prolapsed** intervertebral disc, via the **sinuvertebral nerve**.

The Sinuvertebral Nerve

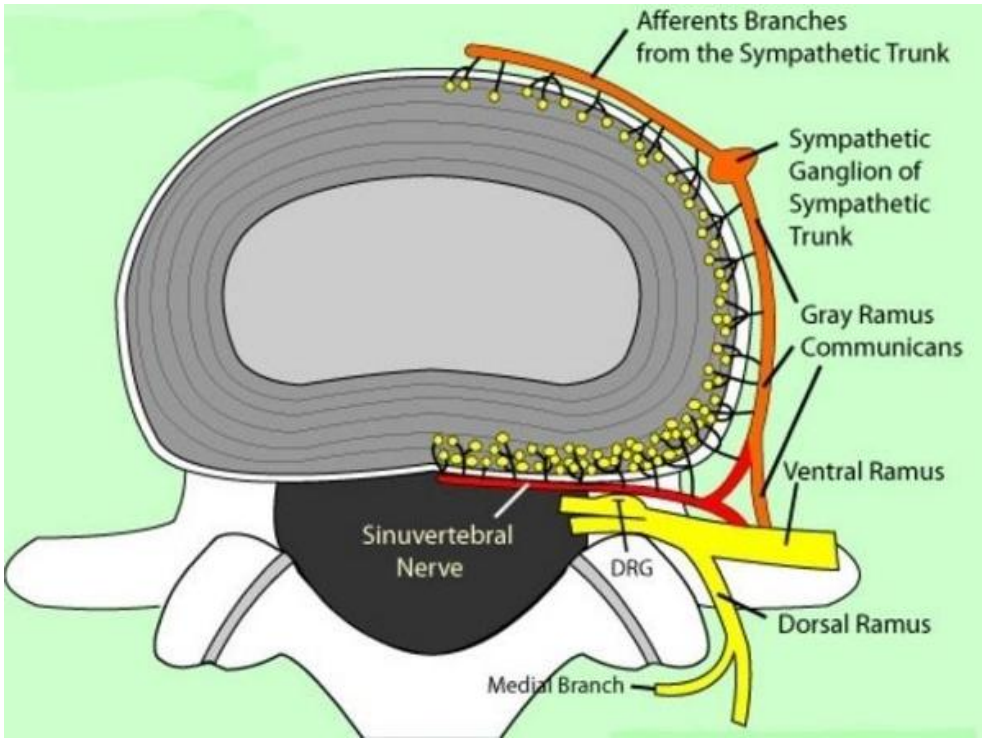


Figure 19 Innervation of a lumbar intervertebral disc

The sinuvertebral nerve is a nerve of the **sympathetic nervous system** (fig 19). The intervertebral disc receives its sensory nerve supply from the **autonomic nervous system**, specifically the sympathetic nervous system. Here the nociceptors around the outer periphery of the intervertebral disc are more concentrated along the **posterior** and **posterolateral** areas of the disc. This can infer that more pain is ‘felt’ from lesions in these areas. Mind you, I have seen significant lesions of the anterior aspect of the disc as well. But, if there are less nociceptors there, do we just feel less

pain (if a tree falls in the forest but there is no one there to hear it, how do we know it fell)?

As you recall from your physiology, the sympathetic nervous system has its motor centre in the **medulla** of the brainstem. The motor nerves then pass down through the spinal cord, where they emerge only between T1 down to L2. From these 14 pairs of roots, they pass into and form the sympathetic chain (of ganglia) on either side of the spine. This structural anatomy is of significance as, if the nociceptors around the periphery of the disc receives its sensory nerve supply from the sympathetic nervous system, the fibres supplying L5 intervertebral disc must receive it nerve supply from the level of L2. If that sensory information wants to get back into the spinal cord 'to report', it must pass back via L2.

Here, if the nociceptive input is strong enough, it will 'overflow' and express itself as a **sensory pain** from the **dermatome of L2.** Here it will be:

- Low back
- Iliac crest
- Outside of the top of the thigh,
- Top of the front thigh towards the groin (see fig 20)

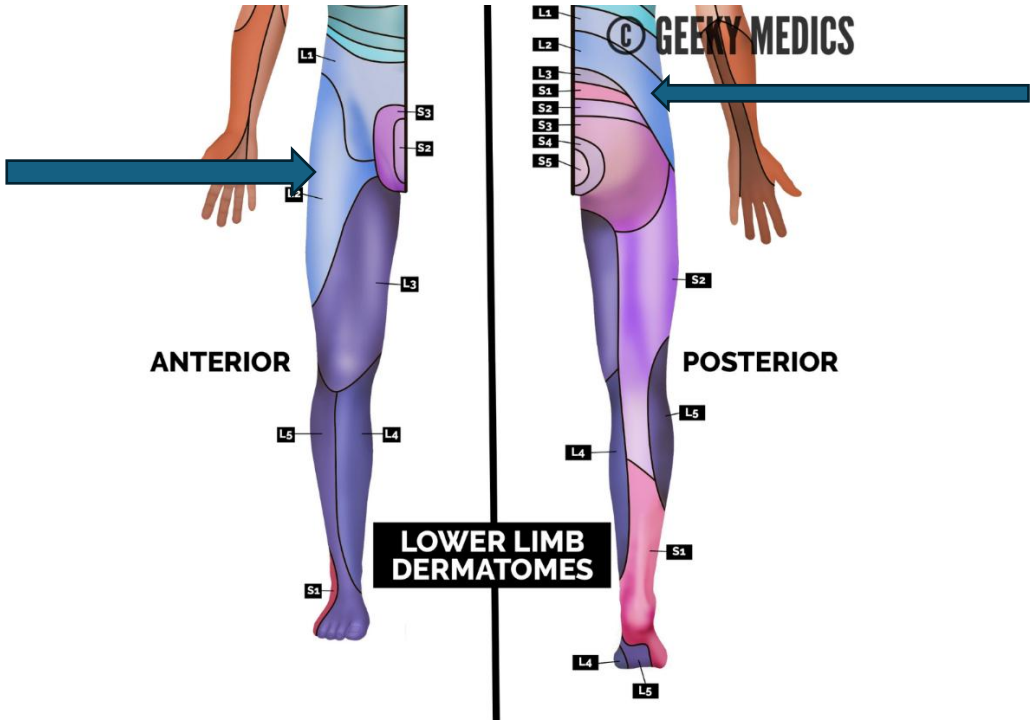


Figure 20 Dermatome of L2

I have thought about this at length, and I wonder if a person can experience a **low-grade** referral pattern, such that the person experiences the referral pattern along the **dermatome**. However, as it continues giving them pain, then the **somatic system** starts to 'join in' with **muscle guarding**. If this situation persists for a while,

then that affected part of the body begins to establish its own **reflex system** to protect and maintain it. Then a chronic situation develops.

Phantom limb pain

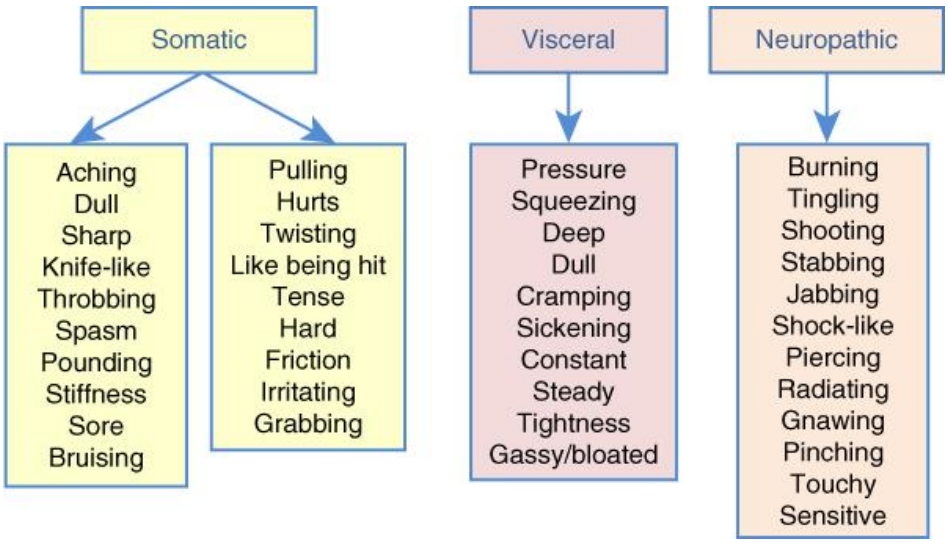
Phantom limb or illusory pain is the experience of pain **without** any signals from nociceptors. It occurs in a subject with previous injuries such as amputation in which the dorsal roots are literally absent from the cord. Even though **no sensory signals** can enter the cord, the subject often feels **extreme pain** in the denervated parts of the body. For example, an **amputee** will often apparently feel pain in a part of his body that has been removed.

The phenomenon of phantom limb pain is a common experience after a limb has been amputated or its sensory roots have been destroyed in which the pain is felt in a part of the body that no longer exists. Pain from an amputated arm is referred to the viscera as a result of disruption to the “balance” between different peripheral inputs to the dorsal horn. A complete break of the spinal cord also often leads to a phantom body pain below the level of the break. The source of phantom pain is complex and not well understood. It has been suggested that there may be abnormal discharges from

1. The remaining cut ends of nerves which grow into nodules called neuromas
2. From overactive spinal neurons
3. From abnormal flow of signals through the somatosensory cortex, or
4. From burst-firing neurons in the Thalamus.

Summary of pain patterns

Table 8 Summary of sources of pain patterns



Headaches

A headache is a poorly understood type of pain that can be either acute or chronic. There are about 300 different types and causes of headaches. The following are some categories of disorders associated with headaches:

- Intracranial structural disease
- Infectious disease
- Cerebrovascular ischemia
- Cerebral vein thrombosis
- Metabolic disease
- Toxic exposures
- Medications
- Extracranial pressure disorders
- Sinusitis
- Vasculitis and collagen vascular disease
- Hemorrhage (parenchymal and subarachnoid)
- Trauma
- Withdrawal syndromes
- Severe hypertension
- Dental, cranial vault, TMJ, and myofascial disorders
- Cervical spine and occipitocervical junction disorders

All that, without having a tight neck!

Thalamic Pain

- Stroke or occlusion in the artery, which supplies the lateroposterior half of the thalamus, can result in a **thalamic lesion**, which is often accompanied by neurologic conditions several months after the initial event.
- The condition is associated with a devastating **intracranial pain** in the **contralateral side** of the thalamic lesion and sensory loss.
- In some cases, severe facial pain is experienced without any sensory loss. The pain resulting from an intracranial lesion is also termed "**central pain**."
- Lesions in the spinothalamic tract and its targets of termination are usually complex. They can induce alteration of **sensory, motor** and **endocrine components** because of the functional diversity of the thalamus. Subjects with this syndrome experience **spontaneous aching** and **burning pain** in body regions where sensory stimuli normally do not lead to pain.
- Because the brain and the spinal cord **do not** contain nociceptors, the pathological process presumably directly stimulates nociceptive pathways, or it prevents the activation of the pain suppression pathways. This condition is known also as **thalamic pain syndrome** or Dejerive-Roussy syndrome.

This latter point is significant, as all the ‘solid’ tissues of the body (the brain, the lungs and the liver) do not ‘feel’ pain. However, the bags and tubes have lots of stretch receptors and chemoreceptors, and thus are more sensitive to pain.

Neuropathic Pain

- Neuropathic pain is a sharp, shooting and devastating pain. It is a persistent pain that arises from functional changes occurring in the CNS secondary to peripheral nerve injury. Once the nerve is damaged, the damaged nerve elicits sustained activation of nociceptors and/or nociceptive afferents.
- Neuropathic pain is due to an abnormal activation of the nociceptive system without specifically stimulating the nociceptors.
- **Neuroplastic changes** occurring in the CNS secondary to the afferent barrage are believed to culminate in CNS neuronal hyperexcitability. Many scientists suggest that “sensitization” of the nervous system following injury is a factor in neuropathic pain (another affecting factor in chronic pain?)
- Neuropathic pain can usually be controlled by anti-inflammatory drugs and opioids. In some cases, such as in diabetics, AIDS, cancer, etc., no treatment or relief is available to neuropathic pain.
- Neuropathic pain should not be confused with **neurogenic pain**, a term used to describe pain resulting from injury to a peripheral nerve but without necessarily implying any neuropathy.

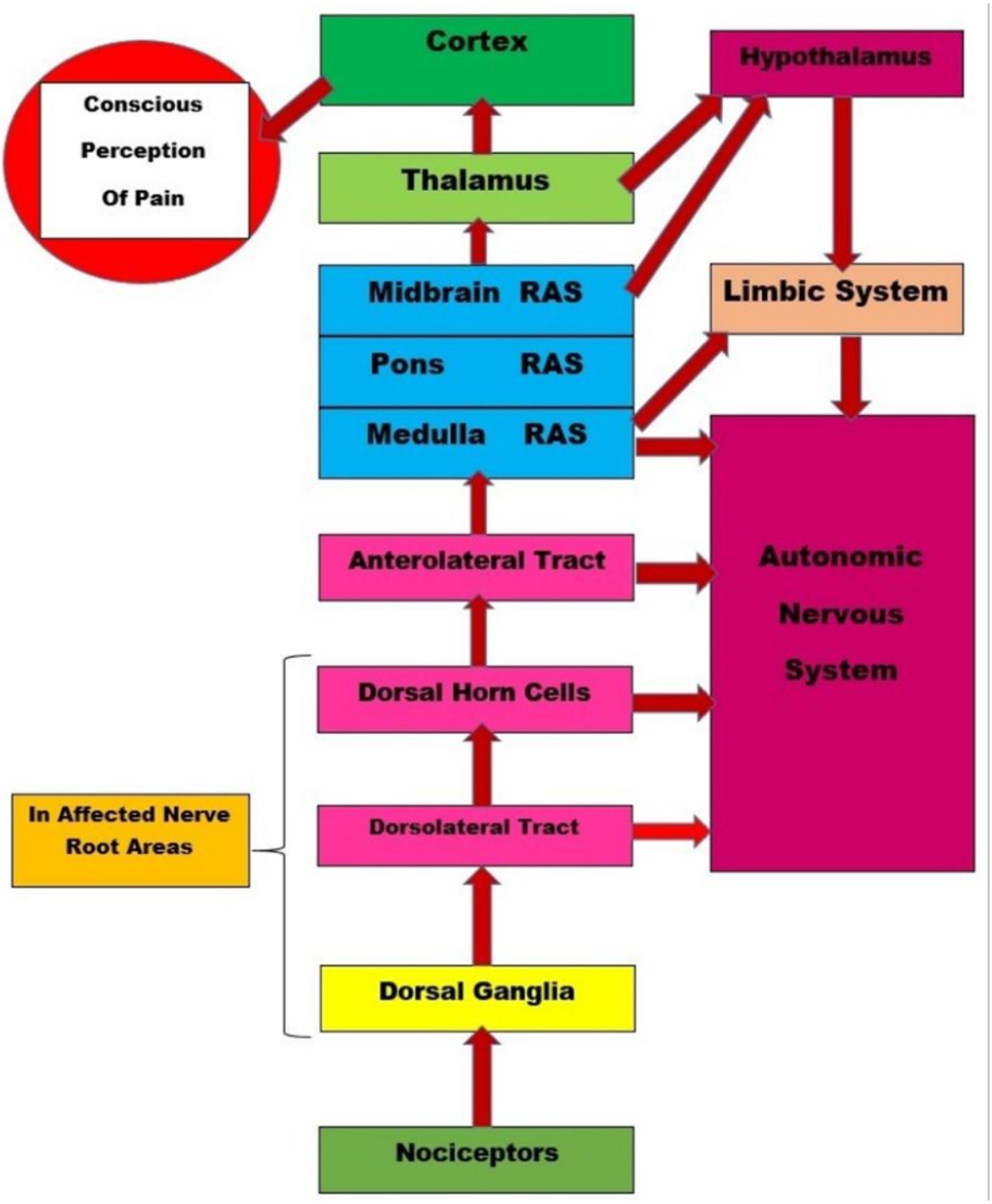
Psychosomatic Pain

Psychic reaction to pain includes all the well-known responses to pain such as anguish, anxiety, crying, depression, nausea and excess muscular excitability through the body.

These reactions vary tremendously from one person to another following a comparable degree of pain stimuli. The sensation of pain can be influenced by emotions, past experiences and suggestions. The same stimulus can elicit different responses in different subjects under the same conditions.

Recently, **Positron Emission Tomography** (PET) has been used to study pain pathways and psychosomatic pain centres. For example, volunteers had their hands dipped in hot water (50° C) while they were conscious. They then dipped their hand again in hot water (50° C) after a post-hypnotic suggestion that the pain would be either more or less unpleasant than the first time. The PET scans of their brains showed that activity in the **anterior cingulate cortex** (part of the **limbic system** – more later) changed in accordance with how unpleasant they **expected** the pain to be. However, the intensity in the primary somatosensory cortex remained constant (i.e., the emotional component of pain is independent of its sensation).

From all that, here is a ‘flow diagram’ of pain pathways;



Chronic Pain

Chronic pain is a persistent pathological condition that **no longer** serves a biological protective function and has become a pathology in itself. It can result from nerve damage or an underlying disease, such as diabetes, cancer, or certain autoimmune disorders. Chronic pain is prolonged pain lasting for **months** or longer that arises from tissue injury, inflammation, nerve damage, tumour growth, lesion or occlusion of

blood vessels. Chronic or inflammatory pain can sensitize (see "Sensitization" below) the nervous system, evoking chemical, functional, and even structural changes that serve to “prime the pain-processing pump”.

Patients suffering from chronic pain may exhibit cognitive deficits, mood alterations, and behavioral changes. Chronic pain is frequently accompanied by psychological states such as anxiety, depression, and sleep disturbances. A key concept in understanding chronic pain is neuronal plasticity. Adaptive changes occur in the nociceptive pathways, leading to peripheral and central sensitization. This sensitization can result in amplification of pain signals, lowered pain thresholds, and exaggerated perception of normally non-painful stimuli (allodynia).

Chronic pain, such as lower back pain, rheumatoid and osteoarthritis, and headache (see "Headaches" below) may result from constant inflammatory activity. In some cases, the pain persists long after the injury heals, but there is no orthodox treatment that will eliminate the pain.

Peripheral sensitization occurs when inflammatory mediators are released at the site of tissue injury, sensitizing the peripheral nerve endings, and increasing their responsiveness to noxious stimuli. Central sensitization involves functional changes in the central nervous system, such as increased excitability of spinal cord neurons and reorganization of cortical maps, contributing to the maintenance and amplification of pain perception.

Sensitization

One possible explanation for chronic pain is a phenomenon called **sensitization**. Following continuation and **prolonged noxious** stimulation, nearby **silent nociceptive** neurons that previously were unresponsive to stimulation, now do become responsive. In addition, some of the chemicals produced and released at the injured site also alter the physiological properties of nociceptors.

The nociceptors begin to initiate pain signals **spontaneously**, which causes chronic pain. In addition, weak stimuli, such as a light touch that previously had no effect on these nociceptors, will further activate the nociceptors which result in severe pain signals, even **allodynia**. This phenomenon is referred to as “**peripheral sensitization**.” The outcome of peripheral sensitization results in a greater and more persistent barrage of nerve impulses firing in the CNS.

The persistent barrage of nerve impulses results in long-term changes in nerve cell activity at the level of the spinal cord and higher centers in the brain. This phenomenon is referred to as “**central sensitization**”. It appears that peripheral and central sensitization **persists** after the injury apparently has healed.

The sensitization of nociceptive neurons after injury results from the release of different chemicals from the damaged area. It is known that **substance P** and **calcitonin gene-related peptides** are released from peripheral nerve ending which

stimulates most cells to release algesic substances which further **potentiates** the pain from the injury. In contrast, central sensitization resulting from severe and persistent injury which cause prolonged release of **glutamate** a phenomenon is also termed "**wind up**." This activation produces **hyperexcitability** of the dorsal horn cells and causes "**central sensitization**." Pain experts now agree that treating chronic pain early and aggressively yields the best results and prevents patients from developing physical and psychological conditions that could worsen the pain.

Neurotransmitters

Now I have mentioned a few neurotransmitters, I will need to explain some of these not only as this is how nerves communicate with each other, but only in reference to the dorsal root. When I studied pharmacology (1980!), we learned about neurotransmitters and receptors.

> Some neurotransmitters are **excitatory** and **stimulate** a response in the **target tissue** (a muscle, gland or another nerve).
>
> Others were **inhibitory**, in that they **prevented** excitation of the target tissue.

In the dorsal root, the main transmitters are:

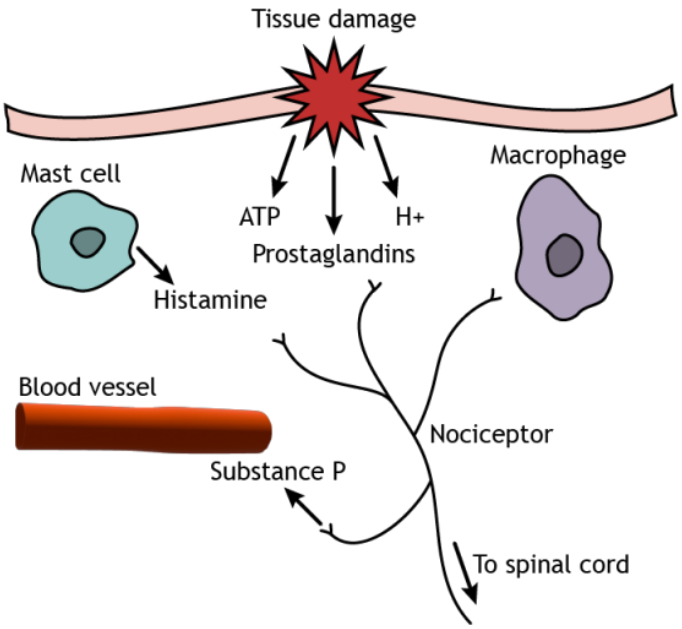
Table 9 Neurotransmitters from sensory nerve fibres

Neurotransmitter	Effect
Substance (P stands for Preparation, or Powder)	A potent vasodilator. Substance P-induced vasodilation is dependent on nitric oxide release. Initiates expression of almost all known immunological chemical messengers (cytokines) Important element in pain perception associated with the regulation of mood disorders (anxiety/ stress) Stimulates cell growth
Glutamate	Is a neurotransmitter and also serves as the precursor for the synthesis of the inhibitory gamma-aminobutyric acid (GABA)
5HT (serotonin)	A neurotransmitter throughout the brain and gut, and is involved in numerous physiological processes

In the end, it might be said, all these had an effect by **eliciting** a response in the cell membrane, and ultimately **within** the cell. Let’s keep it as simple as we can.

First there is the stimulation of the sensory pain nerve (first order neuron). Let us assume here that it is the result of tissue damage. Peripheral mediators produced at the site of injured tissue include:

- Serotonin (5-HT) (from mast cells)
- Kinins (like bradykinin, from mast cells)
- Histamine (from mast cells)
- Nerve growth factors
- Adenosine triphosphate (from cellular damage)
- Prostaglandin (from chemical cellular processes)
- Glutamate (here in reference pain, but serves as a neurotransmitter in many other nerve pathways as well)
- Cytokines (IL1, IL6, TNF)
- Noradrenalin and
- Protons (acid)



Tissue damage causes pain signals to be sent to the CNS but the injured tissue also releases substances like prostaglandins, neurotransmitters, substance P, cytokines, and protons, which cause inflammation and begin the **healing** process. Additionally, non-neuronal cell types such as **mast cells** and **macrophages** come to the injured site, releasing more inflammatory substances. These chemicals, particularly **prostaglandins**, however, can act on nociceptors and cause cellular changes and **increase** the pain felt. All this give us an insight into pain medication and how it works. All these will **depolarize** the membrane of the sensory neuron, eliciting an **action potential** (nerve impulse) along it. This impulse will then pass to the dorsal root of the spinal cord.

It wouldn't be unreasonable to think that Substance P (fig 21) **neurotransmitte**r would act on a Substance P **receptor**. If only life was so easy! The receptor on the post-synaptic membrane is a NK-1 (neurokinin type 1) receptor (see fig 18). Glutamate does act on glutamate, or **NMDA** (N-methyl-D-aspartate) receptor, and 5HT has three types of receptors.

Others are:

Table 10 Peptide neurotransmitters

Amino acid precursor	Neurotransmitter	Physiological effect
Choline	Acetylcholine	Decreased pain perception, pain inhibition, sleep modulation
L-Histidine	Histamine	Inflammation inhibition

5-Hydroxytryptophan	5HT - serotonin	Inflammation inhibition, modulation of pain, mood and sleep cycle
Serine	D-Serine	Increased sensitivity to opioids
Arginine	Nitric oxide	Stimulation of production of natural opioids
Glutamine	Gamma amino butyric acid - GABA	Modulation of sleep and anxiety
L-Glutamic acid	Glutamate	Pain. Stimulation of the mind

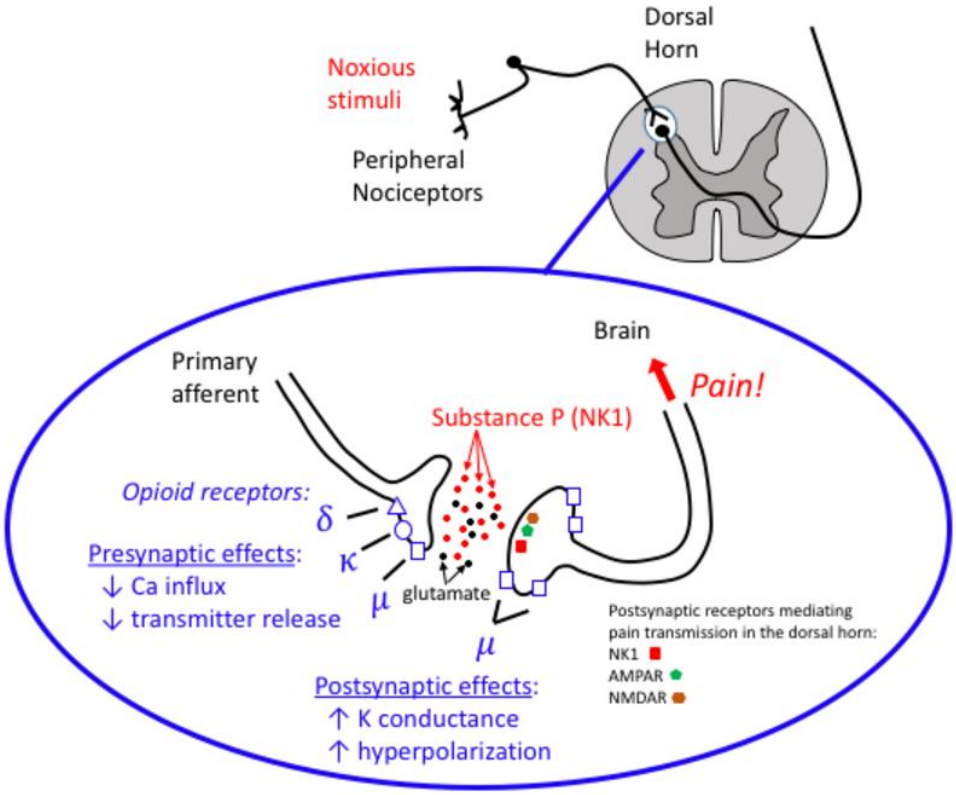


Figure 21 Neurotransmitters at dorsal root

Yes, we hurt ourselves through trauma. We then automatically put our **hand** to the site of trauma, to either exert pressure or rub the area. This introduces the **pain gate theory.**

Pain Gate Theory

This was first proposed in 1965. The gate control theory of pain states that when a stimulus is sent to the brain, it must first travel to the spinal cord. It first goes to the **substantia gelatinosa** (via Lissauer's tract) in the dorsal horn. The substantia gelatinosa of the spinal cord's dorsal horn serves to **modulate** the signals that go through, acting like a "*gate*" for information traveling to the brain. A 'normal' pain pathway passes along Aδ and C fibres. They enter the dorsal root and synapse with the second order neuron, causing an action potential in it.

One tract we haven't mentioned is the **DCML** (dorsal column medial lemniscus) on the posterior of the spinal cord white matter (fig 8). Its first order neuron comes from **Pacinian corpuscles** via the Aβ fibres. They convey sensory information about **deep touch, (**non-noxious stimuli). They then synapse with the second order neuron. Which passes up the **ipsilateral** side of the spinal cord, then decussates at the **medulla** (fig 22)

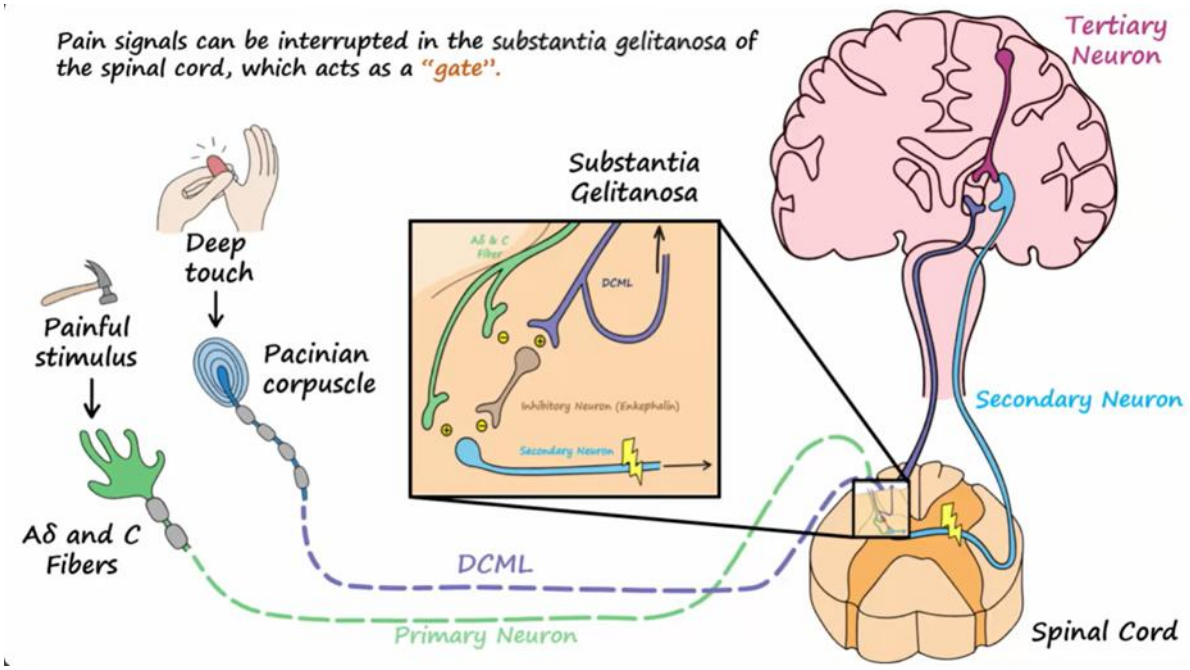


Figure 22 Pain gate theory overview

Coming back to the dorsal root horn, once again. Looking at fig 20, we can see the pain entering via the Aδ and C fibres (green). We can also see the Aβ fibres (purple), before they enter the DCML. There we can see a small branch synapsing with an **interneuron** (a small neuron between two other neurons) in the dorsal horn. The neurotransmitter of this neuron is **Gamma Amino Butyric Acid** (GABA). The effect of this is to **block** the impulses passing between the first order neurons of the Aδ and C fibres and the second order neurons. The result of this is a **reduction of perceived pain**.

Seeing this in an expanded picture (fig 23), it can expand on what I said earlier regarding neurotransmitters being **excitatory** or **inhibitory**. The synapse between the first order Aδ and C fibres are excitatory to the second order neuron. The stimulus from the non-noxious afferents through the Aβ fibres cause the release of **GABA** from the interneuron and are **inhibitory**. Hence, it is the summation of these that brings about the **overall** stimulus to the second order neuron, and GABA acts as a **neuromodulator**.

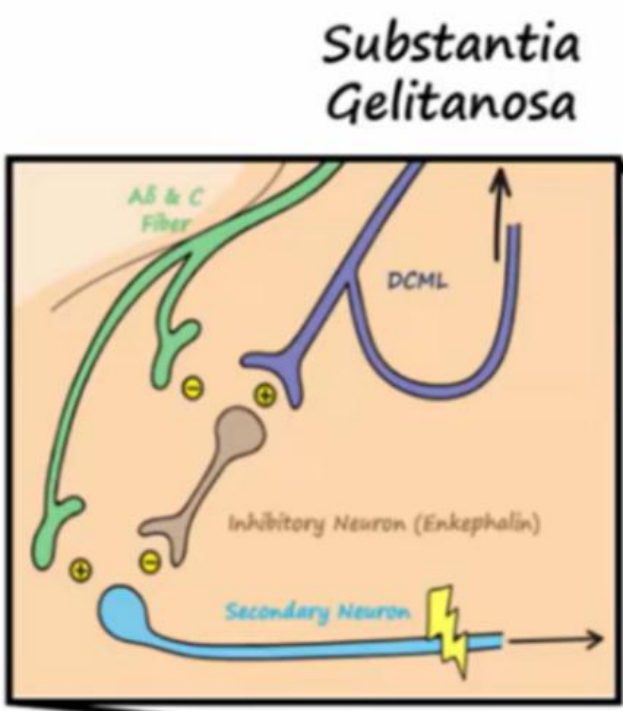


Figure 23 gate control theory - expanded

Another type of neuromodulator is **opioids/opiates.** Exogenous opiates have been around as long as people have been smoking opium. It was such a powerful analgesic that scientists eventually began to realise that, if it has such a profound response in the body, then we must have receptors **specifically** for it. If we have receptors for it, then we must have our own **endogenous** opioids.

The opiate receptor was discovered in 1973 and **enkephalin** (aka endorphin - endogenous opiate) was discovered in 1975. The opiate system is found mainly in the sensory side of the nervous system, brain stem and frontal cortex.

Once a pain signal from the ascending pathway reaches the cerebral cortex, it can trigger the **descending** pain modulatory system. The goal of this pathway is to allow the organism to function enough to respond to the pain source by reducing the pain signal through neuronal inhibition through a the "top down" modulation of pain. It begins in the **periaqueductal gray** (PAG – found around the Aqueduct of Sylvius, between the third and fourth ventricles), an area of grey matter in the midbrain that is involved in the descending pain control pathway. The PAG, receives pain information, processes the nociceptive information and relays it to the medulla. These neurons in the medulla then send a signal down the spinal cord and activate the endogenous opiate system to suppress pain. This ‘top down’ pain control was noticed during WWII at Anzio. The objective of achieving the beachhead was of such import to the allies, that soldiers were coming in with horrific injuries, but were experiencing very little pain.

The descending neurons, from the PAG, use neurotransmitters 5HT and nor-adrenaline. The diagram (fig 24) shows just one neuron but I’m sure they would have

one of each! These descending neurons would synapse with both the first and other interneurons.

The 5HT would **inhibit** the release of Substance P and glutamate from the first order neurons (lees perceived pain)

The nor-adrenaline would **stimulate** the opiate interneurons to release **enkephalin**. This would act on both the first order neuron and the second order neuron – having an **inhibitory** effect on both (less perceived pain)

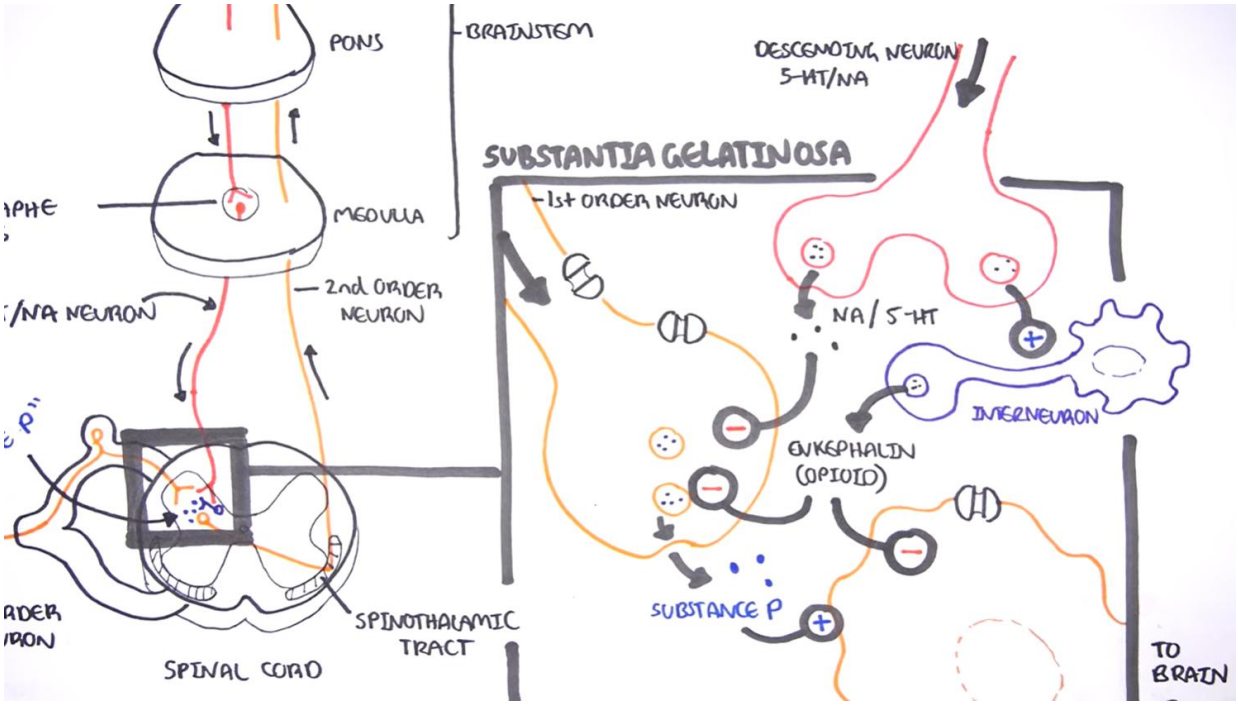


Figure 24 Descending pain control pathway.

Following the discovery of the structure of morphine, and subsequently its synthesis, many types of opiates and opioids have been developed. The ‘problem’ with the opiate system of the body is that there is a ‘knowledge’ of much activity is supposed to be going on. Hence, if exogenous opiates are used regularly, the system will adapt. It will remove, or turn off, opiate receptors, resulting in the need for **more** to gain the same effect. This can lead to dependency.

This is why opiates are only used in acute situations, and sparingly if prolonged used is required.

The details here on nerve pathways and the neurotransmitters create opportunity for the development of drugs, such that we may gain a beneficial effect with regards to pain.

Drugs Used in Pain

An **analgesic** or painkiller is any member of the group of drugs used to achieve analgesia, *relief from pain*.

Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from **anaesthetics**, which temporarily affect, and in some instances completely eliminate, sensation. Analgesics include paracetamol, the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and oxycodone.

In choosing analgesics, the severity and response to other medication determines the choice of agent; the World Health Organization (WHO) pain ladder specifies mild analgesics as its first step.

Analgesic choice is also determined by the type of pain: For neuropathic pain, traditional analgesics are less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as **tricyclic antidepressants** and **anticonvulsants**.

Contraindications

There are several classes of analgesic drugs. Each class has a different history of use for treating different sorts of pain and in different sorts of people. It is difficult to make a statement about when such drugs should be avoided.

In general, pain medication should not be used when there is another, less risky alternative. At the same time, people in pain should not experience under-treatment of pain. When a treatment is available to address the pain, a health care provider should recommend that correct treatment and not a lessor treatment which leaves too much pain.

Classification of analgesics

Broadly speaking, analgesics can work centrally or peripherally:

Table 11 Sites of action of peripheral analgesics

Site of Action	Drug
Peripheral	NSAIDS Local anaesthetics Opioids (dorsal root ganglion)
Central Nervous System	Opioids Antidepressants Anticonvulsants Paracetamol Anaesthetics

Non-Narcotic Analgesics

Generic	Brand Name
Paracetamol	Panadol, Calpol, Kapake, Paralief, Solpadol

Paracetamol

Paracetamol is a medication used to treat pain and fever. It is typically used for mild to moderate pain. In combination with opioid pain medication, paracetamol is used for more severe pain such as cancer pain and after surgery. It is typically used either by mouth or rectally but is also available intravenously. Effects last between 2-4 hours. Paracetamol is classified as a mild analgesic. Paracetamol is generally safe in recommended doses. It only acts centrally (hence, no patches)

Non-Steroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs), function through inhibition of an enzyme, *cyclo-oxygenase*, reducing the production of **prostaglandins** and other inflammatory cytokines. {prostaglandins were first discovered in semen. It was thought to come from the **prostate gland**, hence called prostaglandins. Since then, it has been found in **all** inflammatory processes. Prostaglandin **increases** our perceived pain. Hence reducing it can be analgesic. They are a drug class that groups together drugs that provide **analgesic** (painkilling) and **antipyretic** (fever-reducing) effects, and, in higher doses, **anti-inflammatory** effects. The most prominent members of this group of drugs, aspirin, ibuprofen and naproxen, are all available over the counter in most countries. As analgesics, NSAIDs are unusual in that they are non-narcotic and thus are used as a **non-addictive** alternative to narcotics. Their mode of action is inhibition of the enzyme cyclooxygenase. When I studied pharmacology (1980), there was only one. Now there are two (possibly 3).

COX-1 selective inhibitors

Table 12 COX 1 selective inhibitors

Generic	Brand Name
Ibuprofen	Neurofen, Buplex, Cramp End, Provin
Fenoprofen	Fenopron
Ibuprofen	Advil, Neurofen, Brufen, Buplex, Easofen
Indomethacin	Indocid, Indocin SR, Tivorbex

Non-selective COX 1 and 2

Table 13 Non-selective COX 1 and 2

Flurbiprofen	Fropen
Ketoprofen	Ketocid, Ketovail, Orudis, Oruvail, Powergel, Tiloket
Aspirin	Zorprin, Bayer Buffered Aspirin, Durlaza, Asatab, Adprin-B, , Alka-Seltzer with Aspirin
Anaprox DS,	EC-Naprosyn, Naprelan, Naprosyn

COX-2 Inhibitors

Table 14 Selective COX 2 inhibitors

Generic	Brand Name
Diclofenac	Cataflam, Difene, Voltarol, Diclac
Diclofenac and PPI	Vimovo
Etoricoxib	Arcoxia
Mefenamic Acid	Ponstan
Naproxen	Aleve, Anaprox, Naprosyn
Rofecoxib	Vioxx, Ceoxx, Ceeoxx,

After widespread adoption of the COX-2 inhibitors, it was discovered that most of the drugs in this class **decrease** the side-effect of gastrointestinal bleeding but **increase** the risk of cardiovascular events by 40% on average. I had one male patient with low back pain who said that Ponstan helped. “Did you get that one from your wife?” “Yes. How did you know?” “Because it is only prescribed for ‘women’s things”, I said.

Narcotic Pain Medications (Painkillers)

Table 15 Narcotics - morphine -like drugs

Generic	Brand Name
Buprenorphine	Buprenex, Butrans transdermal patch
Codeine	
Hydromorphone	Dilaudid, Dilaudid-5, Dilaudid-HP, Hydrostat IR, Exalgo ER
Tramadol	Ixprim, Xydol
Meperidine	Pethidine
Morphine	Oramorph; Sevredol; Filnarine; Morphgesic; MST Continus MXL; Zomorph
Oxycodone	OxyContin, Roxicodone, Oxecta, Oxynorm

Narcotics are defined here as drugs that act pharmacologically like **morphine**, a constituent of opium, meaning that they bind to one or more opioid receptor subtypes and change the psychic and physical status of a person—**reduce pain** (analgesia), induce sleep, alter mood or behavior (e.g., euphoria).

Opioids

Morphine, the archetypal opioid, and other opioids (e.g., codeine, oxycodone, hydrocodone, dihydromorphine, pethidine) all exert a similar influence on the brain opioid receptor system. Opioids mimic the actions of **endogenous** opioid peptides, via opioid receptors and modulate the release of nociceptive neurotransmitters (e.g. substance P, see fig 18)

Adrenergic Alpha (2) receptor stimulants

Table 16 Adrenergic receptor stimulants

Generic	Brand
Clonidine	Catapres

This mimics nor-adrenaline, which is released as part of the descending pain control system from the PAG. It acts back on the Aδ and C fibres, reducing their synaptic activity.

It has been noted that these agents can **enhance** analgesia provided by traditional analgesics, such as opiates, and may result in opiate-sparing effects and so were associated with a moderate decrease in pain intensity, opioid consumption This has important implications for the management of acute postoperative pain and chronic pain states, including disorders involving spasticity or myofascial pain, neuropathic pain, and chronic daily headaches.

Combinations of analgesics

Analgesics are frequently used in combination, such as the paracetamol and codeine preparations. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for allergy sufferers.

While the use of paracetamol, aspirin, ibuprofen, naproxen, and other NSAIDS concurrently with weak to mid-range opiates (up to about the hydrocodone level) has been said to show beneficial synergistic effects by combatting pain at multiple sites of action, several combination analgesic products have been shown to have few efficacy benefits when compared to similar doses of their individual components. Moreover, these combination analgesics can often result in significant adverse events, including accidental overdoses, most often due to confusion that arises from the multiple (and often non-acting) components of these combinations.

Table 17 Combinations of analgesics

Generic	**Brand Name**
Paracetamol, and Caffeine	Butalbital
Femcet, Fioricet, Esgic, Esgic-Plus	
Aspirin, and Caffeine,	Fiorinal
Paracetamol, caffeine, and codeine phosphate	Fioricet
Hydrocodone and Ibuprofen	Hydrostal IR, Vicoprofen
Morphine/Naltrexone	Embeda
Paracetamol and Codeine	Capital with Codeine, Margesic #3, Phenaphen with Codeine, Tylenol with Codeine
Paracetamol, Codeine Phosphate, Hyoscine hydrobromide, caffeine monohydrate	Feminax
Codeine, paracetamol, caffeine	Syndol

Local anaesthetics

Local anaesthetics (e.g. bupivacaine and lidocaine) produce local analgesia by reversibly inhibiting action potential propagation in sensory fibres. They also act on motor and autonomic fibres and so can cause motor weakness and autonomic changes. High plasma concentrations of local anaesthetic can cause serious CNS and cardiovascular toxicity.

Anaesthetics

Table 18 Anaesthetics

Generic	Brand name
Half nitrous oxide and half oxygen	Entonox

Neuromodulators

Table 19 Neuromodulators

Generic	Brand
GABA analogue	Lyrica

Gaba-type drugs act via the interneuron between the Aδ and C fibres. It results in **less** Substance P being released, so **less** second order neuron activity.

Cannabis

I have come across some people who find **cannabis** effective as an analgesic, but not everyone. The strangest thing about cannabinoids (endogenous cannabis-like compounds) is that they act as **neuromodulators** and, pharmacologically, act **presynaptically**. However, no nerve uses it as a neurotransmitter – it is synthesized and released from the post-synaptic membrane. What stimulates this? The jury is still out.

Also, regarding opiates and cannabinoids, it is curious how we, as animals, have receptors (therefore have endogenous chemicals) for chemicals in **plants**.

Non-pharmacological treatments for neuropathic pain

Transcranial magnetic stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive, safe process that uses an electromagnetic coil to create a magnetic field. This generates transient magnetic pulses that can activate the brain cortex and pass through the skull with minimal hindrance. These pulses alter cortical excitability at the site of stimulation and as mentioned earlier, also have synaptic effects in distant regions. Repetitive has been found to enhance motor and cognitive functions, as well as reduce depressive symptoms in various disorders including stroke, Parkinson’s disease, and major depressive disorder. It has also been reported to have pain-reducing effects in other

pain-related conditions. The areas of the brain associated with pain perception include the hypothalamus, amygdala, thalamus, somatosensory cortex, insula, ACC, and prefrontal cortex. The specific locations targeted include the orbital frontal cortices, anterior cingulate, medial thalamus, and periaqueductal grey matter. TMS also modulates chronic pain by activating descending inhibitory neural pathways at the dorsal horn level.

Transcutaneous Cutaneous Nerve stimulation (TENS) activates a complex neuronal network to result in a reduction in pain. At frequencies and intensities used clinically, TENS activates large diameter afferent fibres.. This afferent input is sent to the central nervous system to activate descending inhibitory systems to reduce hyperalgesia. Specifically, blockade of neuronal activity in the periaqueductal grey (PAG), rostral ventromedial medulla (RVM) and spinal cord inhibit the analgesic effects of TENS showing that TENS analgesia is maintained through these pathways. In parallel, studies in people with fibromyalgia show that TENS can restore central pain modulation, a measure of central inhibition [6]. Therefore, TENS reduces hyperalgesia through both peripheral and central mechanisms. I have met people who use this regularly and they report that is effective, but only whilst the machine is in operation.

Pain – acute and chronic

Thus far, we have learned that **acute pain** may well be distressing but has a valuable function, it is a **message** that something is wrong and wants to be listened to. **Chronic pain** is something that has gone beyond that. The pain no longer serves a valuable function and has become a **disease** within itself. In this sense, pain is frequently seen by the sufferer as an *invading entity*.

Chronic pain is a common world-wide problem. It has been estimated that 20% of people experience some type of chronic pain, and chronic pain accounts for more than **two-thirds** of all visits to physicians. A person with chronic pain may have physical implications, such as disabilities and restrictions in movements, and psychological implications, e.g., distress, anxiety, and depression. Additional consequences of chronic pain may be a loss of identity and social isolation. Thus, chronic pain is very challenging to treat due to the fact that it is not only a pain but also a changed life situation which needs to be cared for. This leads to the conclusion that experiencing chronic pain is individual and **unique to the person**, as well as a strategy for consistent treatment in order to adjust to it.

I promised to try to keep it simple, but I couldn’t resist including this diagram to demonstrate the number of ingredients of the chemical soup in inflammation and their receptors.

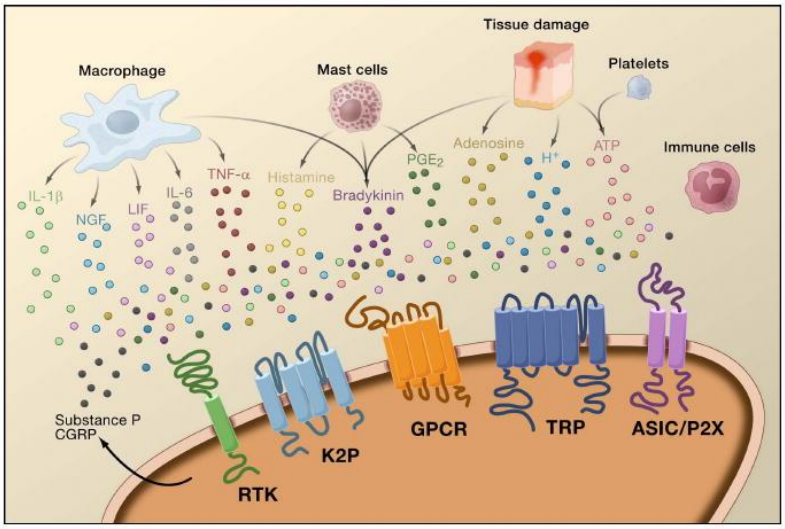


Figure 25 The chemical soup of inflammation

As an experience, chronic pain first affects **one** part of the body and then gradually expands to the **entire sphere** of consciousness, eclipsing everything else in the mind. It frequently can become the singular point of reference in the person's life. Eventually, chronic pain can have a **negative** impact on the mind, where negativity is the opposite of positivity. The sensation of pain is always unpleasant because that **is** the nature of pain, but the **sensation** of pain is not the **experience** of pain which is an alternative insight into the traditional understanding of pain.
Other traditions where pain is associated as something negative include

A person's belief system, like seeing through the eyes of their religion, can be a significant affecting factor. For example, Christian religion, where pain may be understood as a consequence of sin, and medicalization, which has changed our cultural attitude to the point where we have a **fear** of pain, and where pain must be **abolished immediately**. As a result, we may today have less tolerance to discomforts than before. With all this though, pain is a normal life event, and it has an important protective role. For example, CIPA, (Congenital Insensitivity to Pain with Anhidrosis), is a genetic illness which leads to death in early childhood because of inability to **feel** pain.

It can be stated that chronic pain is an illness reflecting how one responds to symptoms or disabilities rather than a disease with objective biological, structural or physiological changes. This can manifest in learning and memory processes, and it may lead to *maladaptive structural* (physical tightness through guarding) and *functional brain changes* (psychological effects) accompanied by possible changes in *body perception*, and it is typically expressed in a behavioural manner (our posture and how we move).

Thus, it is a myth that pain is singularly a signal of tissue damage leading to disability and that the experience of pain can be only by medical interventions. In physiotherapy, there are a number of other myths of pain, for example, "*low pain is a benign, self-limiting condition*"," *all back pain patients are alike*", "*let pain be your*

guide", "*acute and chronic pain are similar*", and "*no pain no gain*". Personally, I have heard all these statements, and I wonder if they are espoused by people who **haven't** experienced chronic pain.

One example of this is the use of the word, "**It**". "**It"** frequently is used by a person who has experienced pain for a while. The pain is seen as an invading entity and is possibly a manifestation of the **cognitive dissonance** (Cartesian, maybe) of the person **separating** themselves from their experience of pain. I confess, I used to say to patients that, "There is no 'it' here, there is only you". Then I had an occasion to fall and break my elbow in 2023. I have experienced pain every day since then. Yes, I used the word '**it'**, at one point. I recalled my own words to my patients, and I have found it incredibly hard **not** to use the word 'it'. Truly, in one aspect of my life and condition, despite my reading of my X rays and seeing the damage therein and my cerebral understanding of my condition, my pain has become a disease within itself.

The aetiology of chronic pain is not fully understood. Unlike Cartesian acute pain, it does not have a protective role by warning of bodily harm. Chronic pain is generally seen as a multifactorial experience which is affected by biological, physiological, psychological, social, and contextual factors. The pathophysiology of chronic pain can be divided into two features:

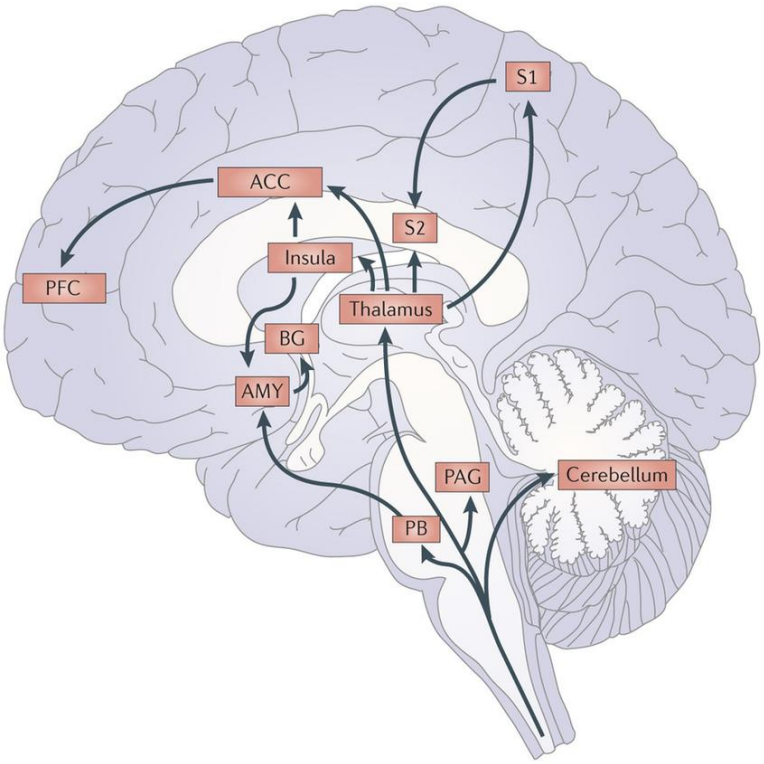
(a) nociceptive pain of musculoskeletal origin and,
(b) neuropathic pain from neural structures.

These features can be in isolation or combination. There is evidence that 20% of incidences of acute pain may transition into chronic pain. Possibly this is because it is not treated properly, but that is not always the case. This point can be of great significance. Speaking personally again. I had a surgical procedure to have some nasal polyps removed some years ago. Instead of taking the opioids prescribed, I opted for the anti-inflammatory route. The nurse there gave me sound advice, "*Stay on top of the pain. If it establishes itself, it can be a pig to shift*". I took this advice on board; I took them prophylactically and didn't wait until I was in pain. I took my pills every 8 hours, to the clock. After just over a week, I realised I no longer needed them.

One major cause of pain is arthritis: osteoarthritis and rheumatoid arthritis. Both are treated with anti-inflammatory drugs. Curiously enough, though, orthodox medicine doesn't classify osteoarthritis as an inflammatory condition, whereas it does with rheumatoid arthritis.

I cited earlier that the study of pain is a study of how the brain works. However, technological advances in magnetic resonance imaging (MRI) and functional MRI (fMRI) pain studies in the 1990s enabled imaging of brain functioning. This might be one of the reasons for the concentration on the brain in pain research at present. Most of the studies are still done with healthy subjects, while many questions for acute pain, and particularly for chronic pain, have remained unanswered.

The fundamental conclusion is that there is no **one** pain centre in the brain, and in chronic pain the brain is not functioning normally; chronic pain being related to other neurological conditions associated with cognitive impairments and behavioural alterations. Furthermore, the reduction in grey matter (cerebral atrophy in older people) may cause an increased perception of pain associated with, e.g., memory and cognitive deficits. Chronic pain is a state where the brain itself can activate pain perception **without** any external stimulation. Brain areas that are active in pain processing in the Neuromatrix of Pain (Fig 25) include the primary and secondary somatosensory cortices (S1, S2), mid cingulate cortex (MCC), insula, thalamus, anterior cingulate cortex (ACC), prefrontal cortex (PFC), basal ganglia, cerebellum, and the brain stem region, particularly periaqueductal grey area (PAG), which are active also in non-nociceptive perception, such as attention, decision-making, motor function, and affective reactions and display a wide range of individual differences.



Nociceptive information from the thalamus is projected to the **insula**, anterior cingulate cortex (**ACC**), primary somatosensory cortex (**S1**) and secondary somatosensory cortex (**S2)**, whereas information from the amygdala (**AMY**) is projected to the basal ganglia (**BG**), **PAG**, periaqueductal grey; **PB**, parabrachial nucleus; **PFC**, prefrontal cortex.

Figure 26 The Neuromatrix of pain

You might recognize these brain areas as elements of cortex (consciousness: S1, S2, PFC, INSULA), limbic system (emotions: AMY), hippocampus (learning: AMY), and the already mentioned PAG and Thalamus.

Neuroimaging (in fMRI) responses to pain can vary even in healthy individuals and by personal experience and can thus only truly be measured by self-report.

Chronic pain can **change** the structure and function of the brain, through **neuroplastination**. In this respect, the changes are to some extent reversible, also through the same principle of plasticity. However, the individual differences in brain structure and function must be accounted for therapy where the focus is on the alteration of central pain memories and maladaptive body perception.

More recently scientists were able to predict how much pain the participants felt by looking at the images of their brains. However, it should be kept in mind that the sensation of pain is different than the experience of pain. As pain is an experience, there is emotional content.

Chronic Pain

Chronic Pain on the other hand, is a persistent pathological condition that **no longer serves** a biological protective function, it has become a disease within itself. It can have underlying facets: for example, nerve damage, or an underlying disease, such as diabetes, cancer, or certain autoimmune disorders. Patients suffering from chronic pain may exhibit cognitive deficits, mood alterations, and behavioral changes. Chronic pain is frequently accompanied by psychological states such as anxiety, depression, and sleep disturbances.

A key concept in understanding chronic pain is **neuronal plasticity**. Adaptive changes occur in the nociceptive pathways, leading to peripheral and central sensitization. This sensitization can result in **amplification** of pain signals, lowered pain thresholds, and exaggerated perception of normally non-painful stimuli (allodynia). With this is sensitivity.

Peripheral Sensitisation

Based on all this, this is a summary of what we have learned so far

Feature	Acute Pain	Chronic Pain
Duration	Short-term, typically resolves after healing	Long-term, persists for months or years
Cause	Direct injury or inflammation	May persist without tissue damage, often due to nervous system changes
Pain Processing	Well-defined pathways; protective	Altered pathways, including central sensitization
Neural Changes	Minimal neuroplastic changes	Neuroplastic changes in both peripheral and central systems
Pain Perception	Localized and sharp	Diffuse, sometimes with emotional or psychological factors
Involvement of the Brain	Involves sensory and motor areas	Involves sensory, emotional, and cognitive regions
Pain Intensity	Proportional to injury	May be disproportionate to the underlying cause or injury

Figure 27 Differences of acute and chronic pain summary

Neuronal Pathways in chronic pain.

Chronic pain has been researched and certain theories have been established. Increased sensitivity of nociceptive neurons in the peripheral nervous system means that stimulation that typically wouldn't cause pain (e.g., light touch) **can** evoke pain responses.

Peripheral sensitization occurs when **inflammatory mediators** are released at the site of tissue injury, causing sensitisation of the peripheral nerve endings, and increasing their responsiveness to noxious and innocuous stimuli. However, with chronic pain, the pain transmission pathway traversing both the peripheral and central nervous systems undergoes significant **plasticity**. This plasticity manifests as sensitization and **exaggeration** (aka hyperalgesia), leading to an **amplification** of pain signals. Chronic pain can also be a potential indicator of underlying pathology such as conditions like injuries, diabetes, arthritis, and tumor growth.

Peripherally induced neuropathic pain (pNP) can contribute to both central and peripheral mechanisms. Recent evidence suggests that the persistence of pNP depends on maladaptive mechanisms in the CNS. In other words, the increased responsiveness in chronic pain could also be explained by the complex localized process of inflammation that occurs after tissue damage and the activation of nociceptive afferent endings in the tissue. This activation is associated with the release of **growth factors, cytokines, prostaglandins, serotonin, and bradykinin**. Due to the presence of sensitizing substances in inflamed tissue, there is increased peripheral sensitivity to painful stimulation.

Role of Calcitonin Gene-Related Peptide (CGRP)

Calcium gene related peptide CGRP is released from sensory neurons and contributes to neurogenic inflammation and pain in conditions like arthritis. It is found in both peripheral and central nervous systems and **enhances** mechanical sensitivity in joint afferents. This leads to increased pain perception during chronic inflammatory states. CGRP signalling **facilitates** synaptic transmission in the spinal cord contributing to the pain and inflammation of chronic arthritis. Activation of CGRP receptors on terminals of primary afferent neurons facilitates receptors on spinal neurons increases glutamate receptor sensitivity. Whereas the cellular effects of CGRP and Substance-P at the level of the spinal cord contribute to the development of **increased** synaptic activity between first and second order neurons in the pathway for pain, the different intracellular signaling pathways also activate different **transcription factors** (changing gene expression). This initiate changes in the expression of genes that contribute to **long-term** changes in the excitability of spinal and maintain hyperalgesia.

CGRP can also be released **antidromically** (from central to peripheral along sensory pathways) in the periphery, increases neurotransmitter release and neuronal responsiveness to noxious stimulation, which leads to central sensitization

underlying chronic pain states. CGRP-containing pathways from the parabrachial nuclear complex in the brain stem), and posterior thalamus convey nociceptive and visceral sensation to the **amygdala** (limbic) and the **insular cortex** (hippocampus). CGRP may be involved in the pathophysiology of inflammatory and neuropathic pain.

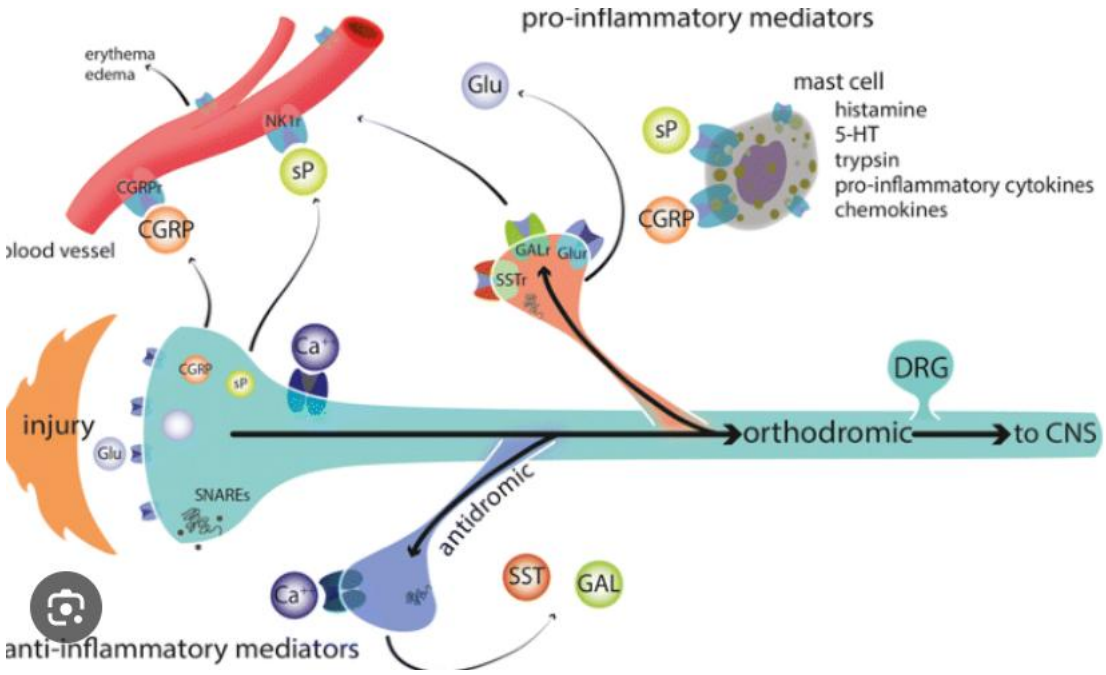


Figure 28 Antidromic pathways

Activation of neurokinin-1 receptors (for substance P) also increases the synthesis of prostaglandins whereas activation of neurokinin-3 receptors increases the synthesis of nitric oxide. Both products act as retrograde messengers across synapses and facilitate nociceptive signaling in the spinal cord.

Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a recently discovered neuropeptide which is present both in the central and peripheral nervous system of adult rats. PACAP modulates neuronal excitability and synaptic transmission, influencing pain and stress responses. It interacts with glutamate receptors, **enhancing** pain signalling pathways, particularly in stress-related pain conditions. PACAP also protects dorsal root ganglion neurons from death and induces CGRP.

While CGRP and PACAP are critical in chronic pain mechanisms, their redundancy and complex interactions may complicate therapeutic targeting, suggesting a need for more nuanced approaches in pain management.

Neuroplastic changes in the peripheral nerve: Over time, there is an increase in the number of ion channels (such as sodium and calcium channels) on the nerve

endings, making them more responsive to stimuli. This results in heightened pain sensitivity even to normally non-painful stimuli (allodynia).

Altered Signaling: Chronic pain often involves alterations in neurotransmitter levels (e.g., increased substance P, glutamate) and receptors (e.g., NMDA receptors), leading to aberrant signaling. In the spinal cord, prolonged or repetitive nociceptive input from the periphery can lead to a phenomenon known as **wind-up**, in which pain signals are progressively amplified. This is mediated by NMDA receptors and other glutamate pathways that increase the excitability of neurons in the dorsal horn of the spinal cord. In chronic pain states, these inhibitory pathways can be diminished, leading to an exaggerated pain experience.

Central Sensitisation

Central sensitization involves functional changes in the central nervous system, such as **increased excitability** of spinal cord neurons and **reorganization of cortical maps** (how the brain re-interprets the periphery) contributing to the maintenance and amplification of pain perception. Amphetamines cause the release of nor-adrenaline and 5HT, hence put the system into a state of ‘stress’. Amphetamines, working back on interneurons in the spinal cord, are also known as analgesics. Moreover, neuropathic pain has been effectively treated with antidepressants such as **tricyclic antidepressants** and serotonin/noradrenaline reuptake inhibitors (SSRI’s and SNRI’s). Selective serotonin reuptake inhibitors (SSRIs) do not effectively treat chronic pain; however, fluoxetine, a selective serotonin reuptake inhibitor, is widely used for nociceptive pain, inflammatory pain, and opioid tolerance and dependency.

Central sensitization and brain plasticity are key processes that contribute to the persistence and amplification of pain signals in chronic pain conditions. The pain receptors become more sensitive (sensitized). Peripheral release of CGRP contributes to the vasodilation of acute neurogenic inflammation.

Spinal Cord Changes

Spinal Cord Changes: Repeated input from injured tissue may lead to changes in the spinal cord, including the facilitation of pain pathways (wind-up phenomenon) resulting in heightened responses to painful stimuli. The archispinothalamic pathway, along with other pathways such as the descending pain modulation pathways, may be involved in chronic pain. In chronic pain conditions. There can be maladaptive changes in the spinal cord and brain that contribute to the persistence of pain signals, even in the absence of ongoing tissue damage.

Regional Brain Changes: Chronic pain can cause structural and functional changes in the central nervous system regions involved in pain processing, such as the expansion or shrinkage of certain brain areas involved in pain processing (neuroplasticity), affecting emotional and cognitive processing related to pain. The anterior cingulate cortex (ACC) is a forebrain structure known for its roles in learning

and memory (hippocampus). Recent studies show that painful stimuli activate the prefrontal cortex, and that brain chemistry is altered in this area in patients with chronic pain

Reduced Inhibition: In chronic pain, there is a decrease in the brain's ability to inhibit pain signals (due to dysregulation of inhibitory neurotransmitters like GABA). This reduces the brain's capacity to filter out irrelevant pain information, leading to an increased perception of pain.

Glial-neuronal interactions

Finally, glial cells, notably **microglia** and **astrocytes**, also contribute to the central sensitization process that occurs in the setting of injury. Under normal conditions, microglia function as resident macrophages of the central nervous system. They are homogeneously distributed within the grey matter of the spinal cord and are presumed to function as sentinels of injury or infection. Within hours of peripheral **nerve** injury, however, microglia accumulate in the superficial dorsal horn within the termination zone of injured peripheral nerve fires. Microglia also surround the cell bodies of ventral horn motoneurons, whose peripheral axons are concurrently damaged. The activated microglia release a panoply of signaling molecules, including cytokines (such as **TNF-α, interleukin-1β and 6**), which enhance neuronal central sensitization and nerve injury-induced persistent pain. Indeed, it appears that microglial activation is sufficient to trigger the persistent pain condition.

The contribution of **astrocytes** to central sensitization is less clear. Astrocytes are unquestionably induced in the spinal cord after injury to either tissue or nerve. But, in contrast to microglia, astrocyte activation is generally delayed and persists **much longer**, up to several months. One interesting possibility is that astrocytes are more critical to the maintenance, rather than to the induction of central sensitization and persistent pain.

The amygdala (fig 29) which is rich in neuropeptides, is associated with the emotional aspects of pain and pain regulation. The hypothalamus, amygdala, and ACC are the main neuroanatomical circuits involved in the regulation of pain. These circuits project to brainstem nuclei such as the **rostral ventral medulla** and **locus coeruleus**, as well as the midbrain **periaqueductal grey**. The transmission of sensory neurons can be altered by internal modulatory mechanisms. Activation of α2-adrenergic, opioid (μ), and cannabinoid (CB1) receptors can modulate the signaling of acute and chronic pain.

Emotional and Cognitive Factors: Chronic pain also affects brain regions involved in mood, emotion, and cognition, such as the limbic system and prefrontal cortex. The emotional distress from chronic pain (e.g., anxiety, depression) can exacerbate pain perception through top-down processing, further influencing central sensitization. Cognitive factors such as attention and expectation can also modulate pain perception, leading to the brain "amplifying" the experience of pain even when the peripheral stimuli remain unchanged.

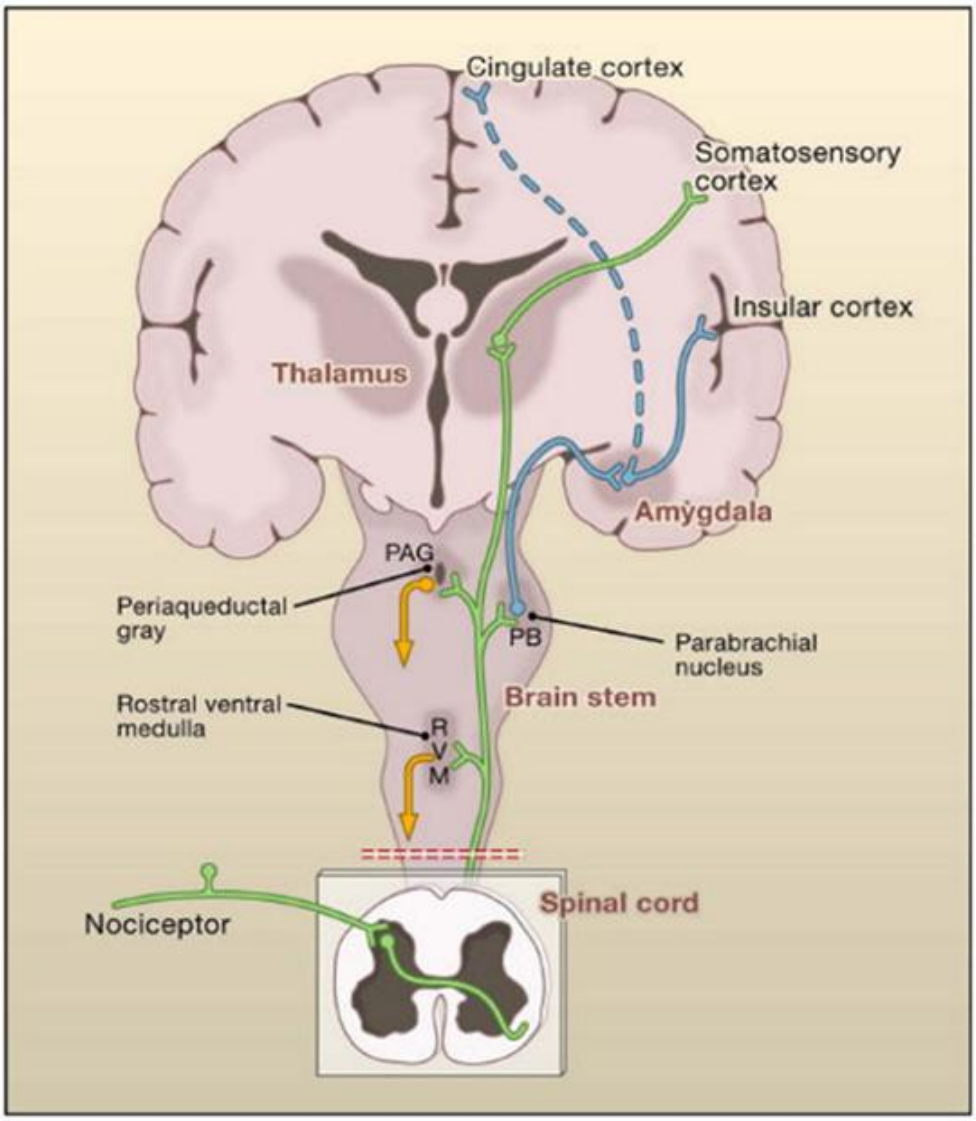


Figure 29 Brain stem, subcortical and cerebral centres

The Biosocial model of pain

The traditional biomedical view has often also been criticized for dualism, keeping social and psychological aspects apart from pain; the 'Cartesian legacy'. In fact, Descartes tried to explain the integration of psyche and soma in more depth, which can be summarised thus: pain is a bodily sensation which prevents more harm or damage and signifies an underlying pathology, and ethics require alleviating pain as much as possible. Despite advances, the orthodox medicine approach has its limitations, such as the following:

(a) the intensity of pain is not proportional to the underlying damage,
(b) recovery of the tissue damage does not necessarily abolish pain, and
(c) the biomedical model does not account seriously for the influence of the psychological and social factors on the experience of pain

Therefore, a more complete understanding of pain was introduced, namely the Biopsychosocial Model, which is presented in Fig 24. Engel described how a negative childhood with emotional and physical experiences may affect a person to become a "*pain prone patient*" suffering from pain without any identified evidence. Engel presented the Biopsychosocial Model of Pain where the emphasis in the assessment and therapy of pain are on the biological, psychological, and environmental factors. The model was widely accepted, partly due to the Gate Control Theory of Pain and also due to the inability of biomedicine to explain and treat chronic conditions.

The problem with chronic pain is the *lack of physical evidence* for pain, which made it imperative to find alternative explanations. This led to a sophisticated model of the Gate Control Theory of Pain, the Neuromatrix of Pain (Fig 24), where pain is produced by the output of a widely distributed neural network in the brain.

The present understanding of the experience of chronic pain involves sensory, affective, cognitive, and evaluative dimensions (Figure 3), which should be taken into

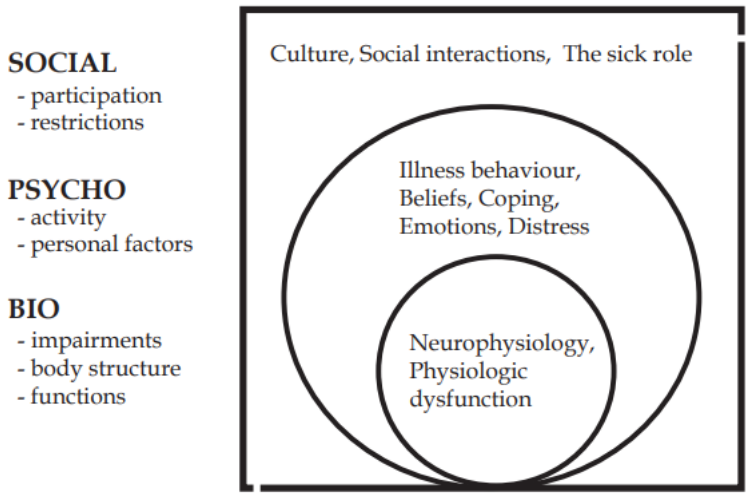


Figure 30 The biopsychosocial model of pain

account in the assessment and treatment of chronic pain (Sim & Waterfield 1997; Sim & Smith 2004). The dimensions can also be regarded as the qualities of the

Measuring pain

Because pain is invisible and immeasurable, its existence, quantity, and quality are difficult to detect, thus the only evidence of the existence of pain is based on the person's own report as a **subjective experience.** On taking a case-history, it is frequently described as a 1 – 10 scale.

Disability and chronic pain

Disability has many definitions, but according to the WHO (World Health Organization, 2014) disabilities covers impairments, activity limitations, and participation restrictions. Chronic pain is often linked with disability due to restriction of movement. There is an assumption is that there is disability due to pain, but this may be a false conclusion. Although pain and disability often go together, **correlation** is not necessarily **causation**. Pain is an experience while disability is restricted activity which is not necessarily caused by pain.

The primary emotions that can be found in chronic pain are distress, depression, fear-avoidance, catastrophizing, and self-efficacy. Distress is commonly observed in persons with chronic pain. It is an overt communication of pain, such as suffering, which can also modulate the experience of pain by amplifying or inhibiting the severity of pain. In chronic pain, depression and anxiety often coexist with psychological distress by affecting each other and predicting more relentless pain

Depression in chronic pain

The prevalence of depression of patients with chronic pain varies from 5% to 100%. Depression has been found to be **more prevalent** in patients with chronic pain than in normal population but in both cases, it is poorly understood. Depression in chronic pain is associated with hopelessness, helplessness, and a feeling of being tortured or punished, and as a direct threat to integrity of the self. Again, the manifestation of depression may not be causal from the pain.

Anxiety in chronic pain differs from fear in that anxiety is an emotion related to cognitive anticipation of a future undesired threat. Fear-avoidance is related to *kinesiophobia* as a fear of physical activity stemming from a belief that it will lead to pain. Avoidance is referred to as a learned behaviour which averts the aversive event. Learned behaviour occurs when the undesirable event has been successfully avoided by certain behaviour.

Catastrophizing is a multidimensional construct comprising aspects, such as rumination, magnification, and helplessness. It is a general or specific cognitive style to physical symptoms including negative thoughts and self-statements about the present and the future. It has been shown that catastrophizing is associated with the experience of heightened pain and emotional distress in response to painful stimuli.

In addition, disability, poorer quality of life, vitality, mental health, and general health were significantly associated with pain catastrophizing.

Treatment of Chronic Pain

Pharmacological treatment Advances in research have contributed to more effective drugs for chronic pain. Some drugs that are used in other illnesses have been found to be effective in chronic pain, such as **antidepressants** for depression and drugs for **epilepsy** but even the most powerful drugs reduce pain by no more than 35% for half of the users, indicating that chronic pain can only rarely be eliminated by currently available medication. Medication is designed to be used only in the short-term, and despite the evidence, many patients persistently use medication without any long-term benefit. It has also been found that those who misuse or overdose medications are more distressed.

Generally, pain killers (analgesic drugs) are at best **ineffective** for long-term use, and at worst they are addictive and have serious side effects causing more pain. The most commonly used medication in chronic pain are NSAIDs (non-steroidal anti-inflammatory drugs), opioids, sedatives/tranquillizers/relaxants, and antidepressants. NSAIDs are effective when they are properly used in **inflammatory** conditions and when used in a combination with opioids in conditions such as **tissue damage**, **postoperative use, cancer pain, arthritis, and migraine**. Typical NSAIDs are aspirin, ibuprofen, diclofenac, and indomethacin. NSAIDs are used more in Finland than in the rest of Scandinavia. Common adverse effects of NSAIDs include gastrointestinal irritation, haemorrhage, anaemia, and increased cardiovascular risks in specific patient populations.

NSAIDs are the most frequently prescribed medications worldwide and are widely used for patients with low back pain. They are effective only for short-term symptomatic relief in patients with acute and chronic low back pain. Perhaps as a result of the widespread use, NSAIDs cause the highest number of reported serious complications among all medications. **Opioids,** such as morphine, codeine, fentanyl, and heroine, are morphine related drugs whose analgesic effect is achieved by the opioid receptors' ability to bind and block the nociception in the spinal cord, midbrain, pons, and in the cortex. They cause **dependence** and development of tolerance, and their withdrawal effects, such as cognitive dysfunction, anxiety, nausea, insomnia, vomiting, and respiratory depression, are the reasons why they are prescribed only for a short-time use in acute pain.

Muscle relaxants can be divided into two main categories, antispasmodic and antispasticity medications. The antispasmodic agents are further sub-classified into

Benzodiazepines	CNS GABA stim: depressants that produce sedation and hypnosis, relieve anxiety and muscle spasms, and reduce seizures	Orphenadrine, chlormezanone, cyclobenzaprine, and diazepam,
Non-benzodiazepines	CNS - GABA	Carisoprodol, metaxalone, zopiclone, and orphenadrine

Although these drugs may relieve skeletal muscle pain, their effects are non-specific and not solely related to muscle relaxation, even though they are prescribed as '**muscle relaxants'**. As pain during the day is something you can probably work around, pain at night just gets in the way – of **sleep**. Sedative drugs are typically prescribed for sleeping problems which are common in chronic pain. They are also recommended for short-time use due to being addictive

Antidepressants, officially called **tricyclic antidepressants**, are frequently prescribed for patients with chronic pain due to their effects on the selective reuptake inhibition of serotonin and norepinephrine, which decrease pain and improve sleep without detected depression. Antidepressants have been postulated to modulate pain through the central and peripheral nervous system. Typical antidepressants are trazodone, imipramine, amitriptyline, doxepin, and nortriptylin. In addition, antidepressants are not sedative and addictive, and the analgesic effect is separate from antidepressant effect. Nevertheless, typical antidepressants' adverse effects are, e.g., problems on men's sexual life, dizziness, insomnia, agitation, cognitive impairments, and disorientation.

Physiotherapy treatment divides the traditional interventions to thermic treatments (heat, cold packs), mechanical treatments (massage, lymph therapy), traction, electro therapy (TENS, transcutaneous electrical nerve stimulation, IF, interferential nerve stimulation, micro wave nerve stimulation, and others, such as DIDY, didynamic nerve stimulation), and hydrotherapy stating that all of these lack evidence of effectiveness in the case of chronic pain.

Exercise therapy is regarded as a remarkable change in physiotherapy where the patient is considered as an active participator who learns new skills and restores impaired ones. Exercise therapy is used in chronic pain against its adverse effects, such as restrictions in movements, dysfunctions or pain on moving, impairments, and consequently deconditioning due to passivity, and immobility.

Taken together, studies show that there is an agreement that exercise helps in the treatment of chronic pain, but it is still not clear exactly to which factors or which particular types of exercises the improvements may be attributed.

Cognitive-behavioural therapy

The relationship between pain and mental health has a long history, but it was not until the last century that mental health practice turned its attention to chronic pain.

The history of cognitive-behavioural therapy to pain management led to publication of a book by Turk et al, which incorporated practical methods from a behavioural approach adding methods from cognitive therapy. Cognitive therapy procedure is a generic term comprising a wide range of approaches consisting of pain education and self-management to improve functioning. I know a counsellor at a college and I asked his opinion of CBT. He was suitably non-committal, saying that it can help in some cases. I read a book on it, and I confess I found it boring and repetitive.

So, you can see that pain has progressed from Descartes. We can re-image his original picture, thus:

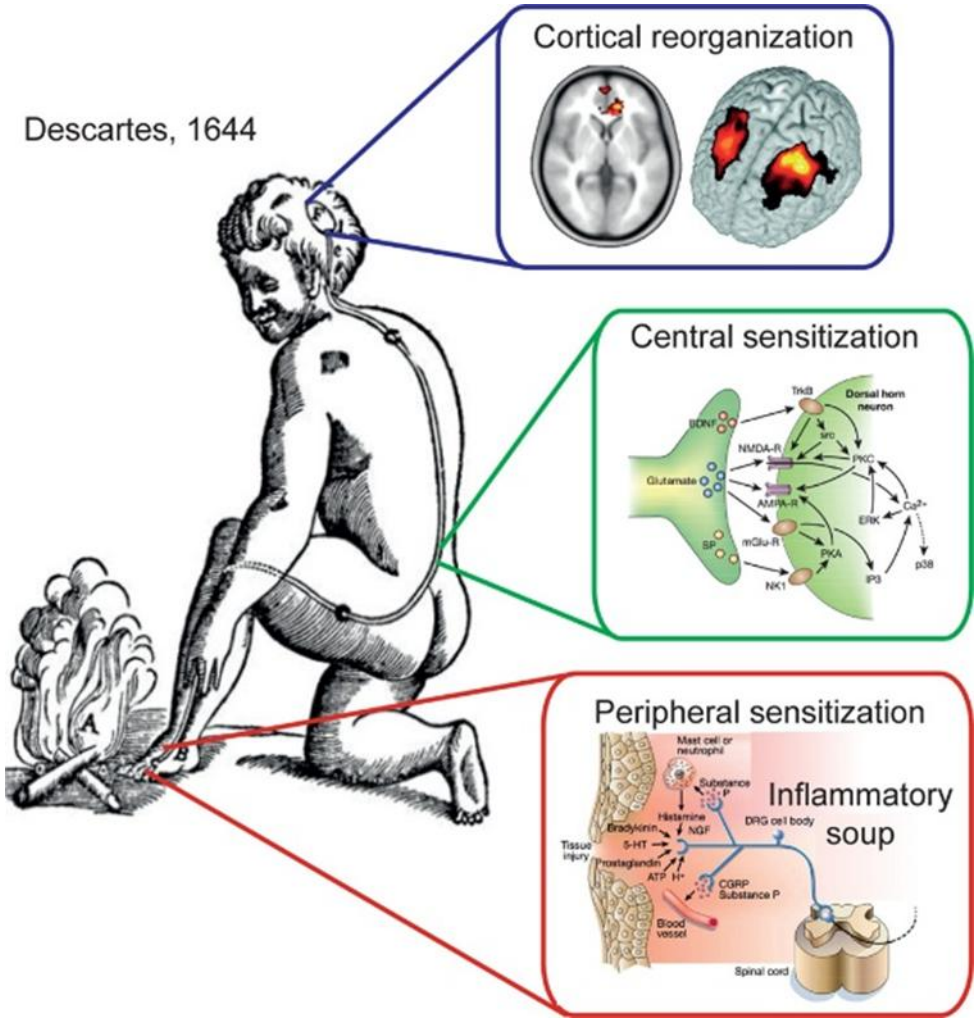


Figure 31 Descartes reprise

To pharmacological and therapeutic practices, in which chronic pain is a personal journey or possibly self-realisation to acceptance-based therapies, which have been proved to be successful in chronic pain treatment. But there is not one therapy that is superior to others. However, the evidence is that acceptance has been found that a

reduction of depression, anxiety, and avoidance and a decrease of the frequency of medical consultations, as well as improved emotional, social and physical functioning and promoting a positive life attitude and commitment to everyday life and higher work status.

The evidence on the effects of medication and physiotherapy is conflicting. Summary of models to understand pain. With all this, you can see there is no consistency in the understanding of pain; instead, pain research is fragmented into several models associated with several research fields. Some disciplinary models to understand and explain chronic pain are presented in Fig 32.

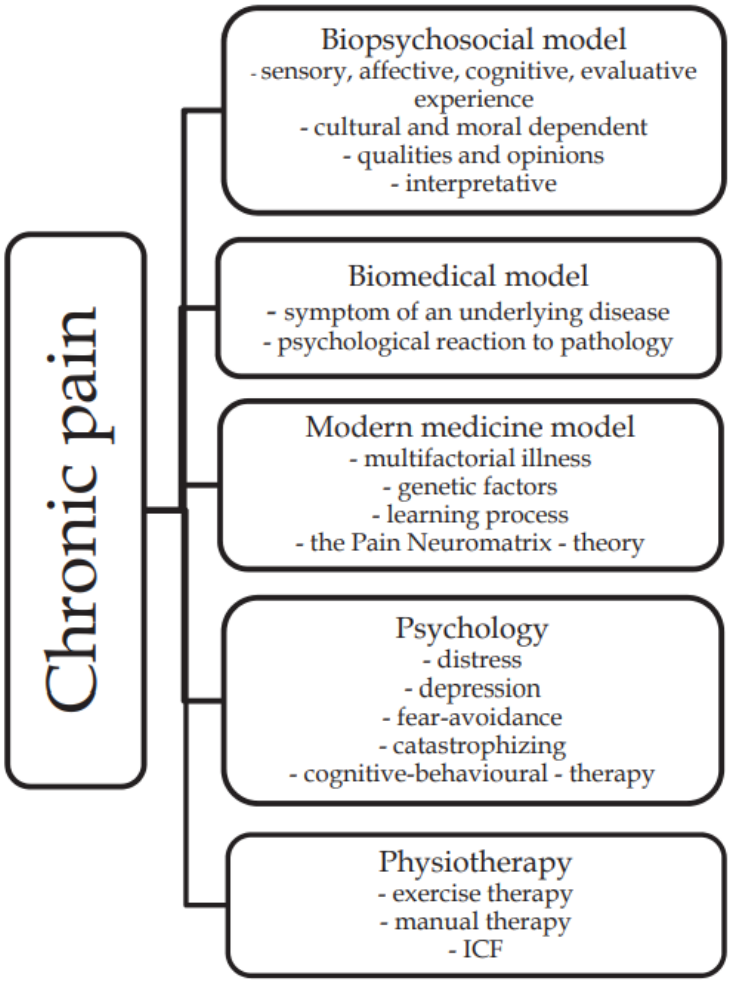


Figure 32 Chronic pain therapy approaches