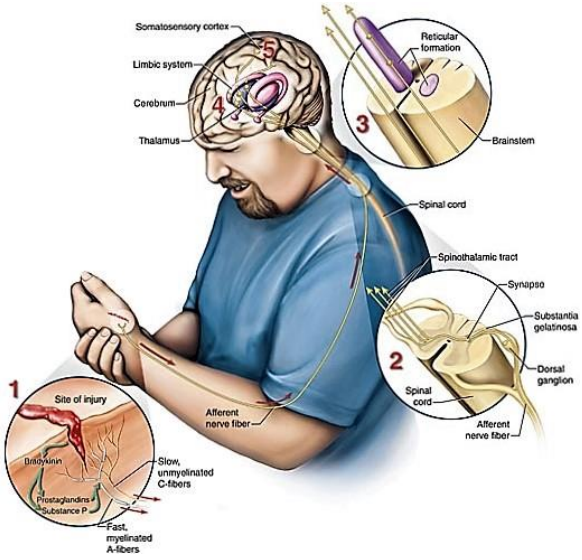
Pain

What is pain?
Neurology of pain
Pain medication

Laurence Hattersley
(2016)



Contents

Pain

What is pain?

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

"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"* (The International Association of the Study of Pain – 1979)

Experiments have shown that rats need **one** experience to learn; humans, possibly an entire lifetime

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*". There were two contraries: pleasure or pain. 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 it is an abnormal stimulation or excessive of normal sensory pathways, you can experience pain.

Descartes wrote just from his own thought processes, but he was writing in the 17th century. He just described how he thought the brain worked how he saw it. He thought the body was a machine. Descartes' book (Traité de Homme - 1664; published 14 years after his death) described how he understood how the nervous system deals with pain of potential injury. At the time the process of the neurological

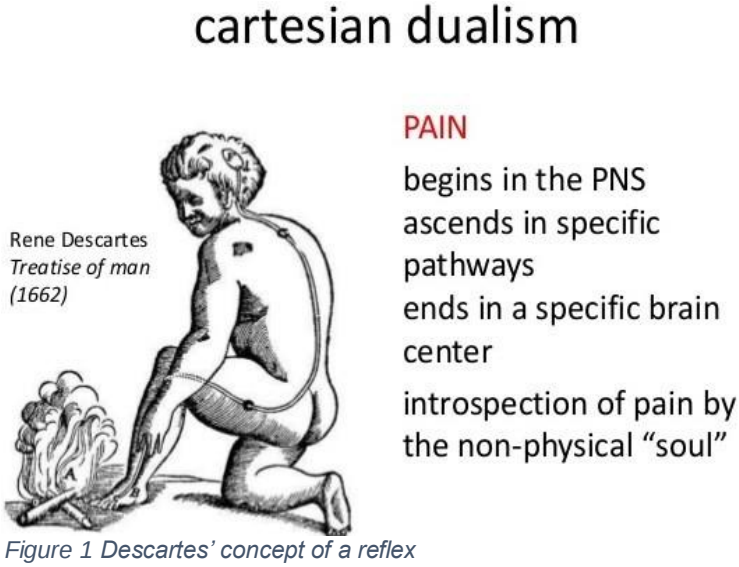


Figure 1 Descartes' concept of a reflex

system was based on mirrors (the neuron wouldn't be described for another 200 hundred years).

Descartes described pain as an 'alarm system'. He described this with this picture of a boy feeling the heat of a fire with his foot. Descartes described the signal passing up from the periphery, up to the brain (he thought it to the pineal gland in the brain, as it was right in the middle) and then reflected down again, causing him to take his foot away from the fire and being burned - and presumably to put some clothes on. This is based upon the presumption that the pain is an alarm signal ("*just as pulling one end of a cord one rings the bell that hangs at the other end*").

So, if you have an injury, or an 'injury producing stimulus', there would be a transmission of events up sensation pathway. Then there would be 'a reflection' of this information into the brain; he thought this to be the pineal gland as it was right in the middle. 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. The model doesn't work with chronic pain, neuropathic pain, phantom limb pain or trigeminal neuralgia.

Pain is ultimately perceived in the brain. Pain is a brain function; it is in the brain. Hence the study of pain, both normal and abnormal, is intrinsic to the scientific endeavour to understand the working of the brain.

Charles Sherrington gave us the concept of ***nociception*** (nocer – to injure or to hurt in Latin), the processing by the nervous of injury related (noxious) signals or events

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, around the body. For any drug (or inherently produced chemical) to have an effect, it has to act via a receptor. For every receptor for a molecule of emotion that exists in your emotional area of your *brain* there are also such receptors in your *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; 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 only applies to consciousness and, more than that, '*good pain'* - the pain that results from injury. But what about the pain of *disease*?

The sensation of pain is unlike any of the other senses we have. All the other senses will habituate; you get used to them. 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 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 is idiopathic. 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 a constant pain is not normal helpful or protective process. Neuropathic pain is very difficult to treat.

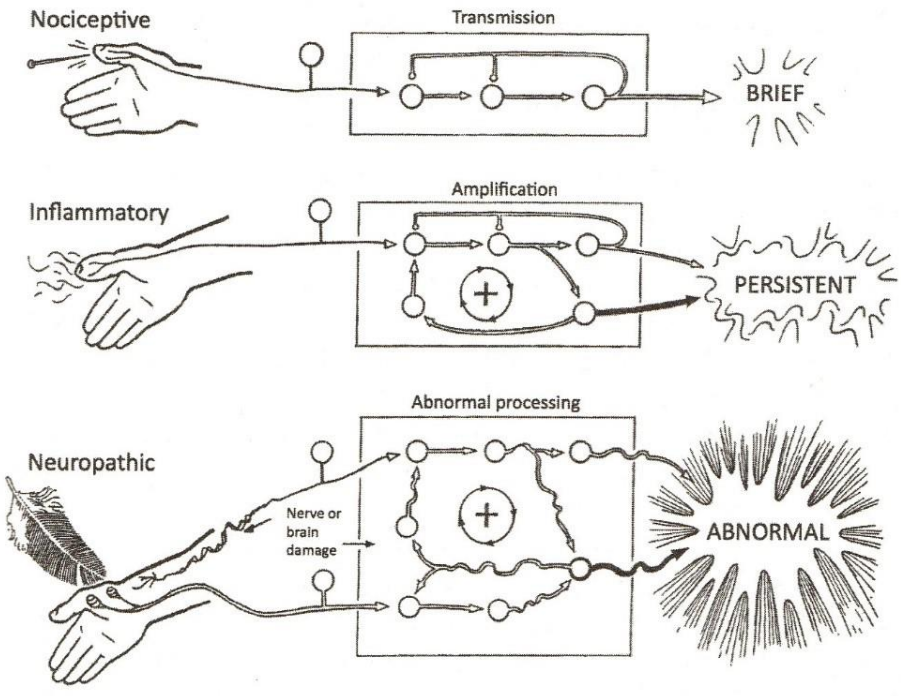


Figure 2 Brief, inflammatory and hyperalgesia pain

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)

Measuring pain

Science has a difficult time trying to measure pain. As it is a *subjective* experience, putting an objective measurement to it is virtually impossible.

I ask patients if the pain is constant or intermittent, to which they frequently say, "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 are lying, it does suggest that the pain has possibly become their only reality.
Another equally difficult question to answer it what **type** of pain it is. I had one man who, when I asked him that question 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 a 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 20,000Hz anymore). But we can only hear the noise if we have functioning hearing (via air conduction - e.g. 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 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 become 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 actually makes *sense of all our senses* is **the brain**. But the information of the sensation has to get there.

The Sense of Touch

There are 5 types of stimuli that can be perceived by the skin

SKIN STIMULI:

- **Tactile** – usually simply called “touch.” Receptors to both touch and pressure are called **Mechanoreceptors.**
- **Pressure** – a “heavy touch.”
- **Temperature** – hot or cold. Receptors to temperature are called **Thermoreceptors.**
- **Pain** – When something is damaging your tissues. Receptors to pain are called **Nociceptors.**
- **Vibration** – an “on-and-off” type of touch.

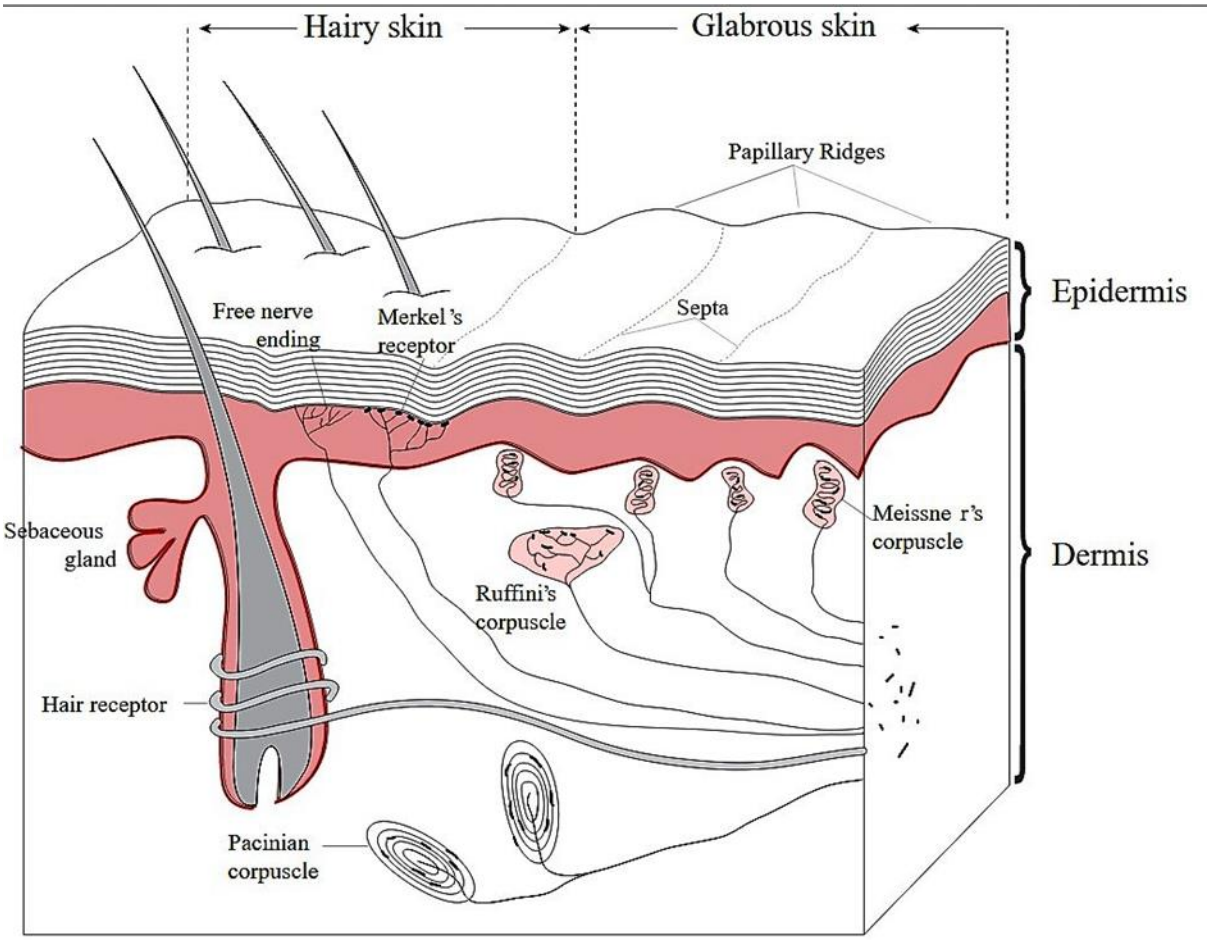


Figure 3 Skin sensory receptors

- **Free Nerve Ending**

They can perceive pain, touch and temperature (less than 20ºC and more than 45ºC). They can be found in the epithelial layer of the skin. Nociceptors are free (bare) nerve endings found in the skin, muscle, joints, bone and viscera.

- **Merkle's disc**

They respond to light pressure. They can be found in the epithelial layer of the skin. They can perceive fine differences in location, a process known as **two-point discrimination**. *(This is what enables people to read Braille with their fingers).*

- **Perifollicular**

They wrap around hair in the skin and they can perceive when the hair on your body or face is being touched.

- **Ruffini corpuscle**

They respond to touch and pressure. They are found deeper within the skin, in the subcutaneous layers. They are known to be sensitive to changes in angle, and as such, they also carry a proprioceptive role involved in telling the brain where the fingers are located in space.

- **Meissner's Corpuscle**

They too are involved in two-point discrimination. They are usually found in the "hairless" portions of your skin such as the palm of your hand and your fingers.

- **Pacinian Corpuscle**

They are sensitive to pressure and vibration. It's the biggest type of nerve ending. In fact it's so big that it can be seen by the naked eye!! They are characterized by a large, flat laminated "disc." They are found deeper within the skin *(this is the reason why they respond so well to pressure)*

I had an accident in 1975 and broke my left thigh. I had surgery and they put in a Küntscher nail. At the top of the incision on my thigh, the surgeon cut the lateral cutaneous nerve of the thigh. The result of this is that I have no light touch on the outside of my thigh. I still feel pressure and pain though. So if a very light tree fell on my leg, it wouldn't 'hear' it.

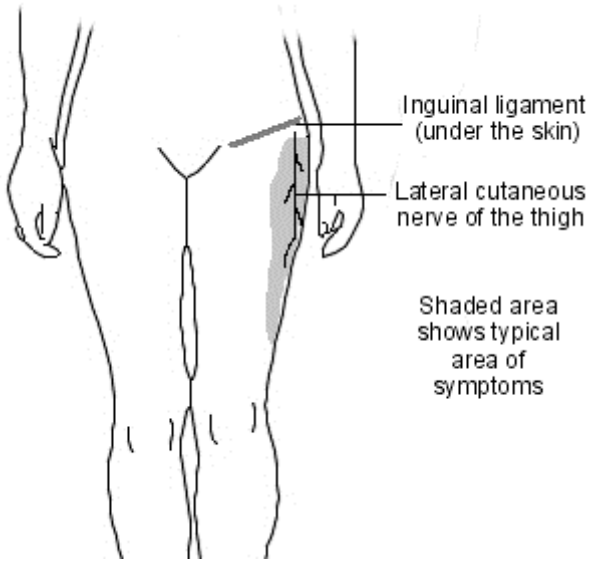


Figure 4 Lateral cutaneous nerve of the thigh

Pain Receptors

Pain is termed nociceptive (nocer – to injure or to hurt in Latin), and nociceptive means sensitive to noxious stimuli. 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 free (bare) nerve endings found in the skin, muscle, joints, bone and viscera. Recently, it was found that nerve endings contain transient receptor potential (TRP) channels that sense and detect damage. The TRP channels are similar to voltage-gated potassium channels or nucleotide-gated channels, having 6 transmembrane domains with a pore between domains 5 and 6. They transduce a variety of noxious stimuli into receptor potentials, which in turn initiate action potential in the pain nerve fibers. This action potential is transmitted to the spinal cord and makes a synaptic connection in lamina I and/or II. The cell bodies of nociceptors are mainly in the dorsal root and trigeminal ganglia. No nociceptors are found inside the CNS.

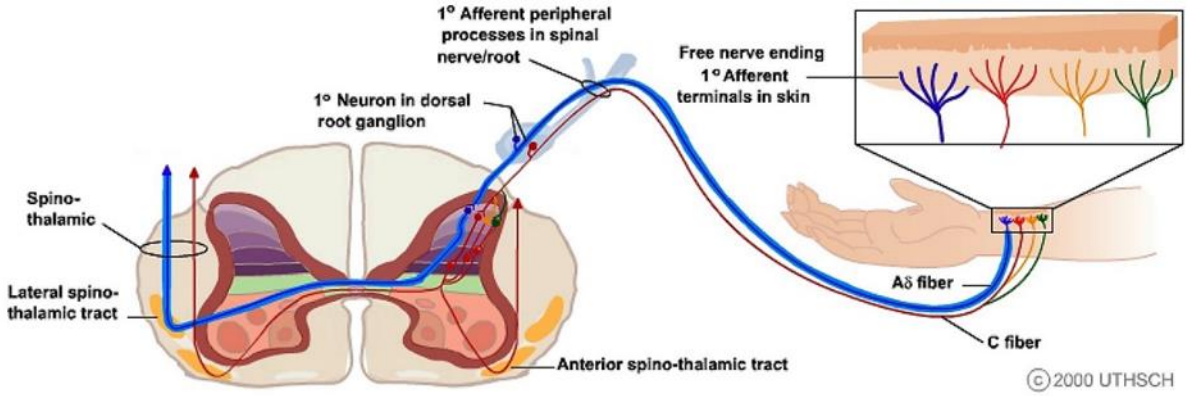


Figure 5 Different nociceptive/free nerve endings, and the fibres carrying pain sensation from the nociceptors to the spinal cord

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. Skin nociceptors may be divided into four categories based on function. The first type is termed high threshold mechanonociceptors or specific nociceptors. These nociceptors respond only to intense mechanical stimulation such as pinching, cutting or stretching. The second type is the thermal nociceptors, which respond to the above stimuli as well as to thermal stimuli. The third type is chemical nociceptors, which respond only to chemical substances. A fourth type is known as polymodal nociceptors, which 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. Many of the fibers 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.

Visceral Nociceptors. Visceral organs contain mechanical pressure, temperature, chemical and silent nociceptors. The visceral nociceptors are scattered, with several millimetres between them, and in some organs, there are several centimetres between each nociceptor. Many of the visceral nociceptors are silent. The noxious information from visceral organs and skin are carried to the CNS in different pathways.

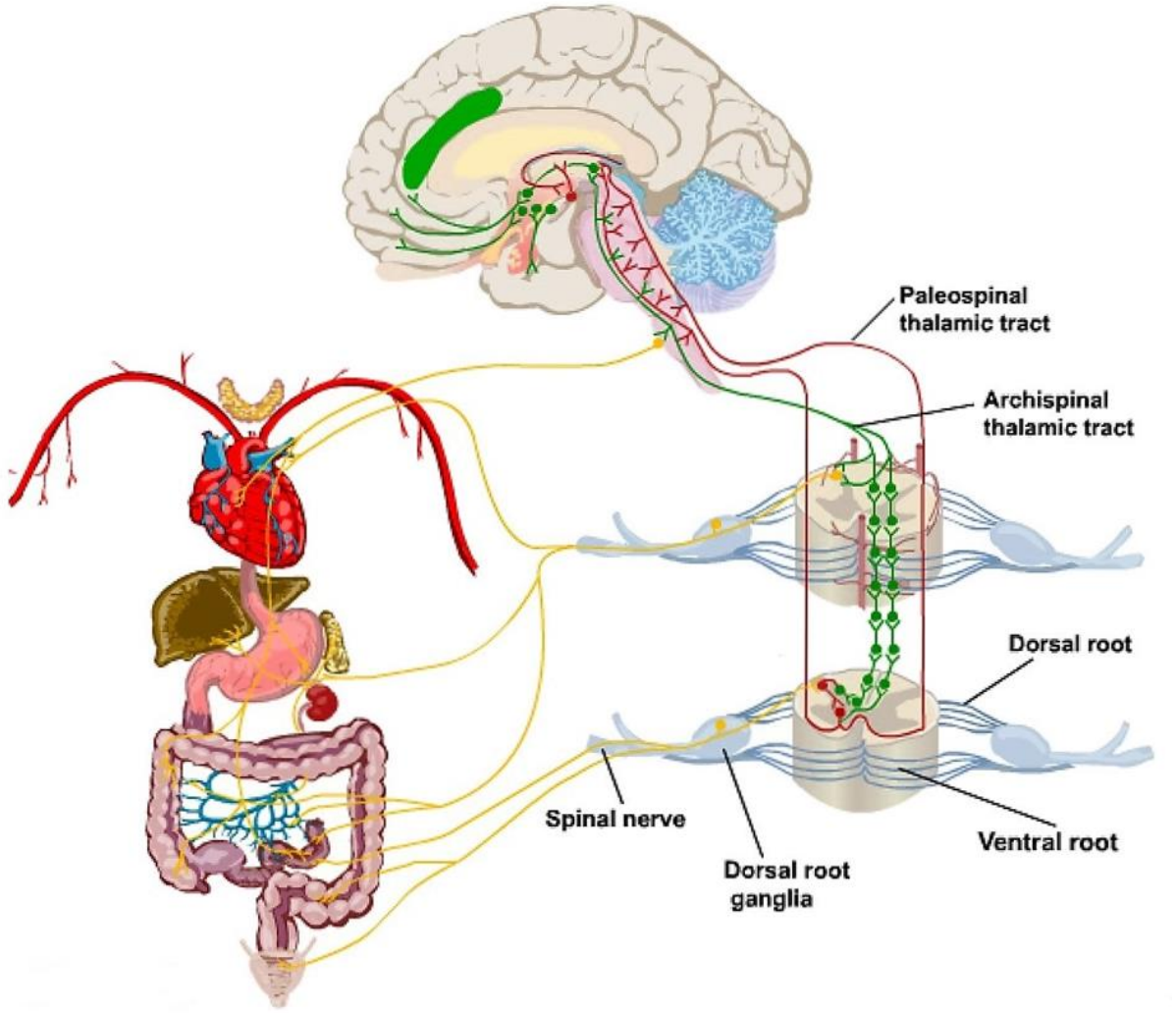


Figure 6 Visceral nerve pathways

Silent Nociceptors. In the skin and deep tissues there are additional nociceptors called "silent" or "sleep" nociceptors. These 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 (see below). Many visceral nociceptors are silent nociceptors.

Factors that Activate Nociceptors

Nociceptors respond when a stimulus causes tissue damage, such as that resulting from cut strong mechanical pressure, extreme heat, etc. The damage of tissue results in a release of a variety of substances from lysed cells as well as from new substances synthesized at the site of the injury. Some of these substances activate the TRP (*transient receptor potential*) channels which in turn initiate action potentials. These substances include:

1. ***Globulin and protein kinases***. It has been suggested that damaged tissue releases globulin and protein kinases, which are believed to be amongst the most active pain-producing substances. Minute subcutaneous injections of globulin induce severe pain.

2. ***Arachidonic acid***. Arachidonic acid is one of the chemicals released during tissue damage. It is then metabolized into *prostaglandin* (and *cytokines*). The action of the prostaglandins is mediated through a G protein, protein kinase A cascade. The prostaglandins block the potassium efflux released from nociceptors following damage, which results in additional depolarization. This makes the nociceptors more sensitive. Aspirin is an effective pain killer because it blocks the conversion of arachidonic acid to prostaglandin.

3. ***Histamine***. Tissue damage stimulates the mast cells to release histamine to the surrounding area. Histamine excites the nociceptors. Minute subcutaneous injections of histamine elicit pain.

4. ***Nerve growth factor (NGF)***. Inflammation or tissue damage triggers the release of NGF. NGF then binds to TrkA (*tropomyosin related kinase A*) receptors on the surfaces of nociceptors leading to their activation. Minute subcutaneous injections of NGF elicit pain.

5. ***Substance P (SP) and calcitonin gene-related peptide (CGRP)*** are released by injury. Inflammation of tissue damage also results in SP and CGRP release, which excites nociceptors. Minute subcutaneous injection of substance P and CGRP elicits pain. Both peptides produce vasodilation, which results in the spread of edema around the initial damage.

6. ***Potassium - K^+***. Most tissue damage results in an increase in extracellular K^+. There is a good correlation between pain intensity and local K^+ concentration.

7. ***Serotonin (5-HT), acetylcholine (ACh), low pH (acidic) solution, and ATP***. These substances are released with tissue damage. Subcutaneous injections of minute qualities of these products excite nociceptors.

8. ***Muscle spasm and lactic acid***. Not only can some headaches result from muscle spasms of smooth muscle, stretching of a ligament can also elicit pain. When muscles are hyperactive or when blood flow to a muscle is blocked, lactic acid concentration increases and pain is induced. The greater the rate

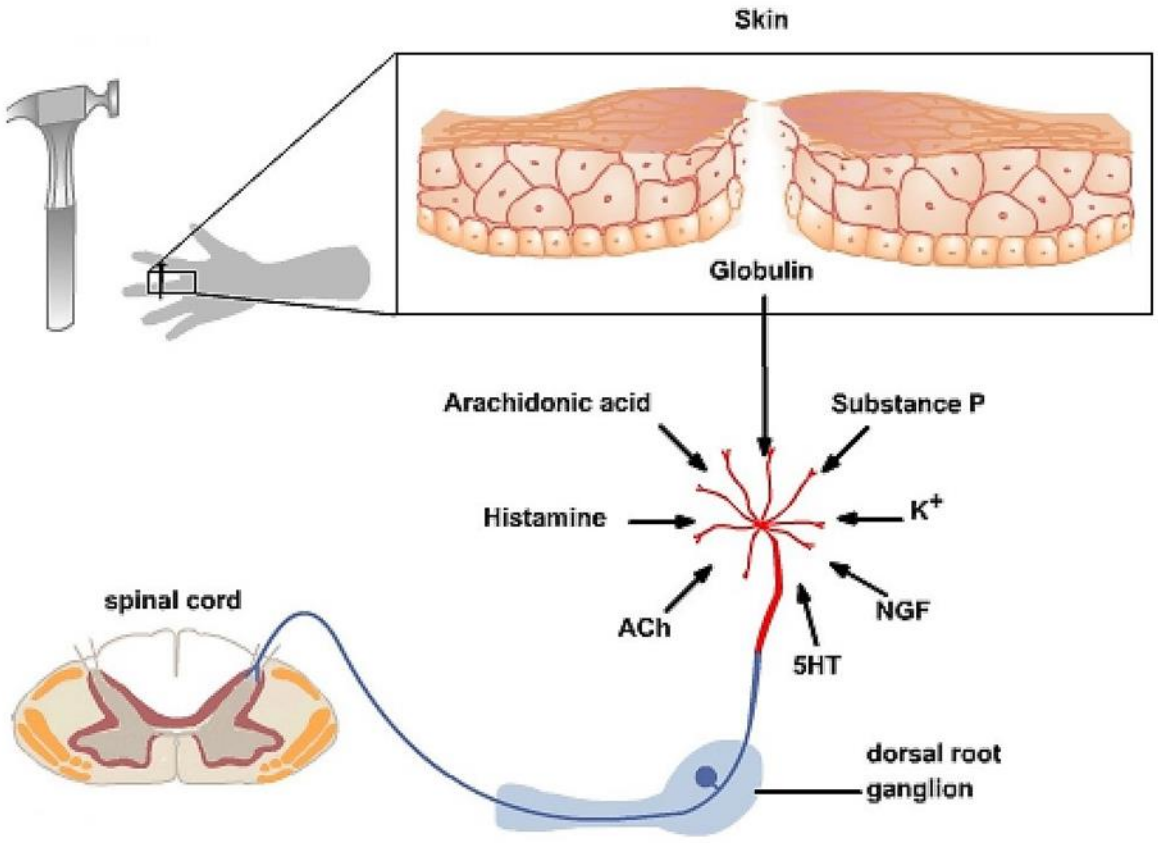


Figure 7 Chemical factors activating nociceptors

Not all the tissues share the same wealth of receptors (with us, particularly pain). The brain has *no receptors at all*. All the solid organs do not have pain receptors, but all the hollow ones (e.g. tubes, gut, and ureter) are richly innervated - ask anyone who has had a kidney stone.

The gut has no pain receptors that detect heat (i.e. burning), 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.

Skin has no receptors for ultraviolet radiation. UV rays cause inflammation in skin (sun burn) so it is the inflammation that is the cause of the pain we feel, through the release of cytokines and the vasodilatation that is a facet of acute inflammation, along with oedema; all of which stimulate the nociceptors.

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.

Research understands that there are several types of afferent nerves fibres:

Afferent Nerves	**GSA**	The **general somatic afferent fibers** (**GSA**, or **somatic sensory fibers**), afferent fibers, arise from cells in the spinal ganglia and are found in all the spinal nerves, except occasionally the first cervical, and conduct impulses of pain, touch and temperature from the surface of the body through the posterior roots to the spinal cord and impulses of muscle sense, tendon sense and joint sense from the deeper structures
Afferent Nerves	**GVA**	The **general visceral afferent fibers** (GVA) conduct sensory impulses (usually pain or reflex sensations) from the viscera, glands, and blood vessels to the central nervous system. They are considered to be part of the visceral nervous system, not the autonomic nervous system. However, unlike the efferent fibers of the autonomic nervous system, the afferent fibers are not classified as either sympathetic or parasympathetic. GVA create referred pain by activating general somatic afferent fibers where the two meet in the posterior horn of the spinal cord (dorsal horn). The cranial nerves that contain GVA fibers include the facial nerve, the glossopharyngeal nerve and the vagus nerve.
Afferent Nerves	**SSA**	**Special somatic afferent** (**SSA**) refers to afferent nerves that carry information from the special senses of vision, hearing and balance. The cranial nerves containing SSA fibers are the optic nerve (II) and the vestibulocochlear nerve (VIII). "SSA" may also stand for "special sensory afferent", but this term encompasses both special somatic and special visceral afferents
Afferent Nerves	**SVA**	**Special visceral afferent** (**SVA**) refers to afferent nerves that develop in association with the gastrointestinal tract. They carry the special senses of smell (olfaction) and taste (gustation). The cranial nerves containing SVA fibers are the olfactory nerve (I), the facial nerve (VII), the glossopharyngeal nerve (IX), trigeminal nerve (V) and the vagus nerve (X). The facial nerve receives taste from the anterior two-thirds of the tongue; the glossopharyngeal from the posterior third. SVA fibers in the vagus originate in the epiglottis and pharynx. The sensory processes, using their primary cell bodies from the inferior ganglion, send projections to the medulla, from which they travel in the tractus solitarius, later terminating at the rostral nucleus solitarius
Fibres	**Ia**	A type Ia sensory fibre, or a primary afferent fibre is a type of sensory nerve. It is a component of a muscle fibre's *muscle spindle*, which constantly monitors how fast a muscle stretch changes. (In other words, it monitors the velocity of the stretch).
Fibres	**Ib or Golgi**	The *Golgi organ* (also called Golgi tendon organ, GTO, tendon organ, neurotendinous organ or neurotendinous spindle) is a proprioceptive sensory receptor organ that senses changes in muscle tension. It lies at the origins and insertion of skeletal muscle fibers into the tendons of

		skeletal muscle. It provides the sensory component of the Golgi tendon reflex.
Fibres	**II or Aβ**	Type II sensory fibre (group Aβ) is a type of sensory fibre, the second of the two main groups of stretch receptors. They are non-adapting, meaning that even when there is no change in muscle length, they keep responding to stimuli. In the body, Type II fibers are the second most highly myelinated fibers. The muscle's instantaneous length, or position, is directly proportional to their firing rate. This information would indicate the position of one's leg once it has stopped moving. They do not respond to rate of length changes as do the Ia fibers.
Fibres	**III or Aδ or fast pain**	An A delta fibre or Aδ fibre is a type of sensory nerve fibre. A delta fibers carry cold, pressure and some pain signals. Because A delta fibers are thinly myelinated, they send impulses faster than unmyelinated C fibers, but more slowly than other, more thickly myelinated "A" class fibers.
Fibres	**IV or C or slow pain**	Group C nerve fibers are one of three classes of nerve fibre in the central nervous system and peripheral nervous system. The C group fibers are unmyelinated and have a small diameter and low conduction velocity. They include Postganglionic fibers in the autonomic nervous system (ANS), and nerve fibers at the dorsal roots (IV fibre). These fibers carry sensory information. Damage or injury to nerve fibers causes neuropathic pain. Capsaicin activates C fibers Vanilloid receptors, giving chili peppers a hot sensation.

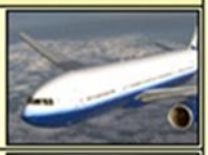
Type of Nerve Fibre	Information Carried	Myelin Sheath?	Diameter (micrometers)	Conduction Speed (m/s)
A-alpha	proprioception	myelinated	13 - 20	80 - 120 
A-beta	touch	myelinated	6 - 12	35 – 90 
A-delta	pain (mechanical and thermal)	myelinated	1 - 5	5 – 40 
C	pain (mechanical, thermal, and chemical)	non-myelinated	0.2 - 1.5	0.5 - 2 

Figure 8 Types of sensory nerve fibres

Over 100 years ago we discovered that pain was carried on **C-fibres**. These are the *thinnest* of the nerve fibres - and therefore the *slowest.* Many of the nociceptors are connected with C-fibres, ***but not all*** C-fibres are connected to nociceptors.

Types of C fibres	
C fibre nociceptors	Responsible for the second, burning pain
C fibre warming specific receptors	Responsible for warmth
Ultra-slow histamine-selective C fibers	Responsible for itch
Tactile C fibers	Sensual touch. Includes CT fibres, also known as C low-threshold mechanoreceptors, which are unmyelinated afferents found in human hairy skin, and have a low mechanical threshold. They have moderate adaptation and may exhibit fatigue on repetitive stimulation and "after-discharges" for several seconds after a stimulus
C mechano- and metabo- receptors in muscles or joints	Responsible for muscle exercise, burn and cramp

Table 1 Types of C-fibres

So, we have nerve fibres. Where do they go from there?

These various sensory signals take two different paths to reach the brain, both of which start in a given part of the body and end in the brain's somatosensory cortex. Each of these paths consists of a chain of **three neurons** that pass the nerve impulses from one to the next. Where these two paths differ is in the location where they cross the midline in the spinal cord.

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 free (bare) nerve endings found in the skin, muscle, joints, bone and viscera. Recently, it was found that nerve endings contain transient receptor potential (TRP) channels that sense and detect damage. The TRP channels are similar to voltage-gated potassium channels or nucleotide-gated channels, having 6 transmembrane domains with a pore between domains 5 and 6. They transduce a variety of noxious stimuli into receptor potentials, which in turn initiate action potential in the pain nerve fibers. This action potential is transmitted to the spinal cord and makes a synaptic connection in lamina I and/or II. The cell bodies of nociceptors are mainly in the dorsal root and trigeminal ganglia. No nociceptors are found inside the CNS.

Remember that in the human body, the nerves responsible for sensory inputs from the left side of the body crosses over and goes to the right side of the brain. From the right side of the body, the impulses pass over up to the left side of the brain. Likewise with motor impulses coming down from the brain: right to left, and left to right (in scientific terminology, they must "*decussate*").

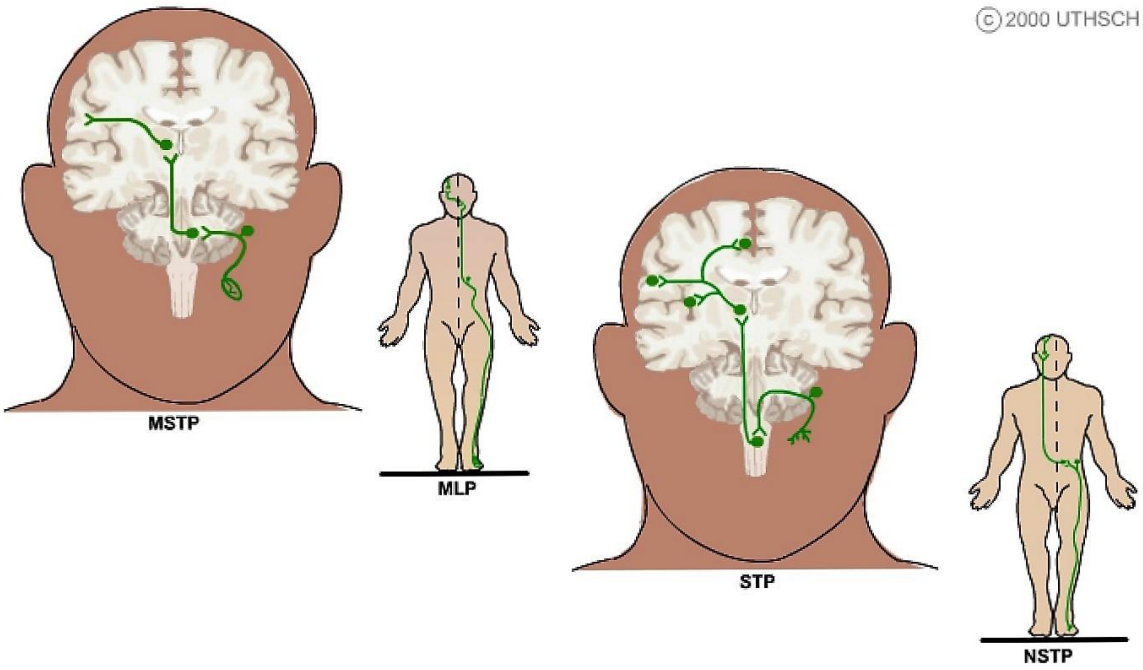


Figure 9 Decussation of nerves

Now let's follow the path that any incoming sensory impulse—whether for touch, pain, heat, or proprioception—follows from the spinal cord to the brain. Regardless of the sensory modality, the three neurons in question form a chain running from one side of the spinal cord to the other, and the cell body of the **first** neuron in this chain is always located in a spinal (dorsal root) ganglion. This neuron is said to be T-shaped, because its axon emerges as a short extension from its cell body and then soon divides into two branches going in opposite directions: one goes to the part of the body that is innervated by this spinal nerve, while the other immediately enters the dorsal root of the spinal cord (an essentially sensory part of the spinal cord, as opposed to the ventral root, which is a motor area). It is from this point on that the two pathways differ.

The pathway responsible for **touch and proprioception** is called the lemniscal pathway. The first axon in this pathway runs along the dorsal root of the spinal nerve and up the dorsal column of the spinal cord. (Along the way, this axon also sends out collaterals: branches in the dorsal root that play a valuable role in the local inhibition of pain, among other functions.)

Pain Pathways

The ascending pathways that mediate pain consist of three different tracts:

- The **neospinothalamic tract**
- The **paleospinothalamic tract** and
- The **archispinothalamic tract.**

The first-order neurons are located in the ***dorsal root ganglion*** (DRG) for all three pathways. Each pain tract originates in different spinal cord regions and ascends to terminate in different areas in the CNS.

Neospinothalamic Tract

The **neospinothalamic tract** has few synapses and constitutes the classical ***lateral spinothalamic tract*** (LST). The first-order nociceptive neurons (in the DRG) make synaptic connections in Rexed layer I neurons (marginal zone). Axons from layer I neurons decussate in the anterior white commissure, at approximately the same level they enter the cord, and ascend in the contralateral anterolateral quadrant. Most of the pain fibers from the lower extremity and the body below the neck terminate in the ***ventroposterolateral*** (VPL) nucleus and ***ventroposteroinferior*** (VPI) nucleus of the thalamus, which serves as a relay station that sends the signals to the primary cortex. The VPL is thought to mainly be concerned with discriminatory functions. The VPL sends axons to the ***primary somatosensory cortex*** (SCI).

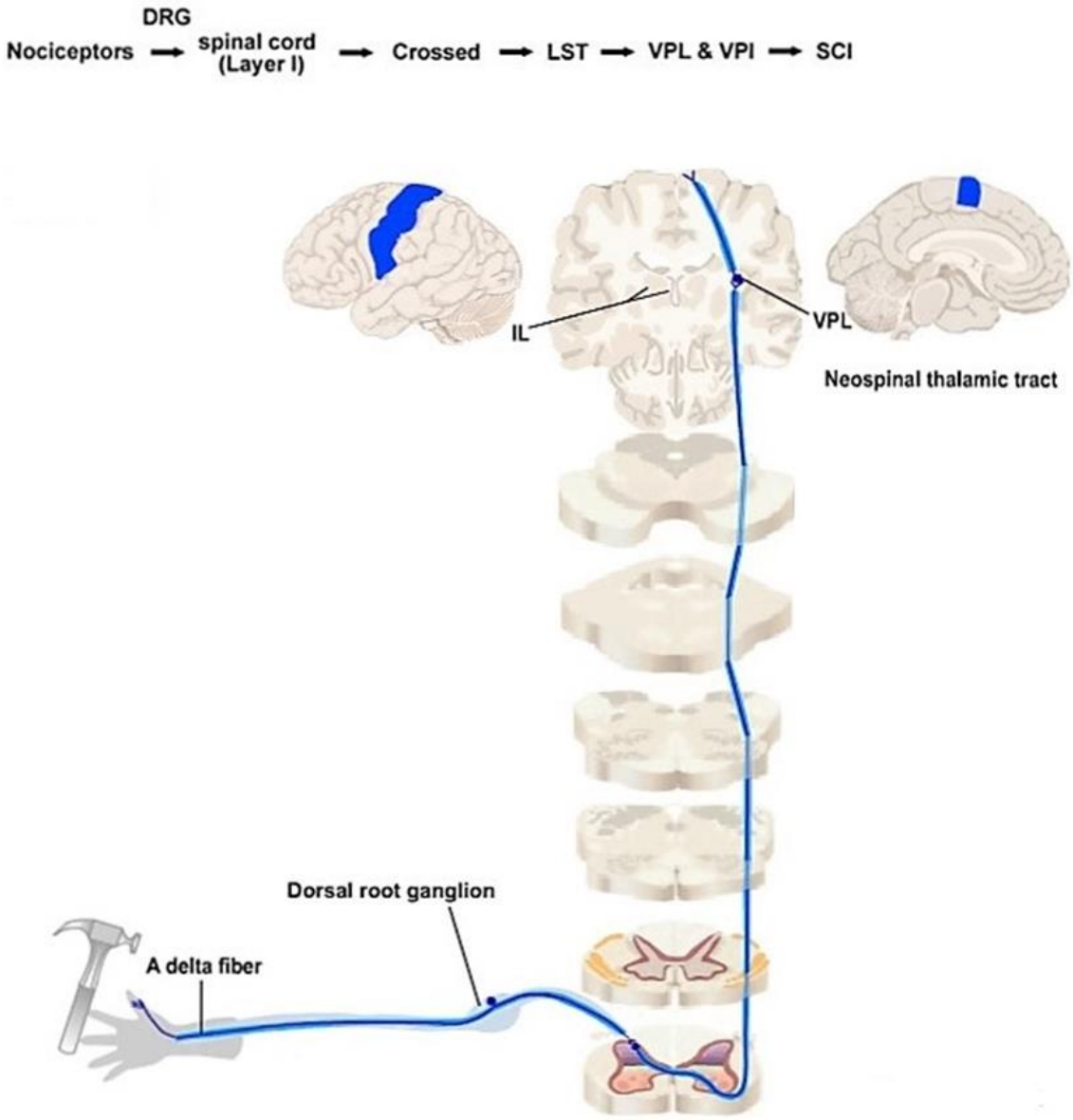


Figure 10 Neospinothalamic pathways

The first-order nociceptive neurons from the head, face and intraoral structures have somata in the ***trigeminal ganglion***. Trigeminal fibers enter the pons, descend to the

medulla and make synaptic connections in the spinal trigeminal nucleus, cross the midline and ascend as trigeminothalamic tract (or trigeminal lemniscus, The A delta fibers terminate in the ***ventroposteromedial*** (VPM) thalamus, and the C fibers terminate in the ***parafasciculus*** (PF) and ***centromedian*** (CM) ***thalamus*** (PF-CM complex). The PF-CM complex is located within the intralaminar thalamus and are known also as ***intralaminar*** (IL) nuclei. All of the neospinothalamic fibers terminating in VPL and VPM are somatotopically oriented and from there send axons that synapse on the primary somatosensory cortex (SC I - Brodman areas 1 & 2). This pathway is responsible for the immediate awareness of a painful sensation and for awareness of the exact location of the painful stimulus.

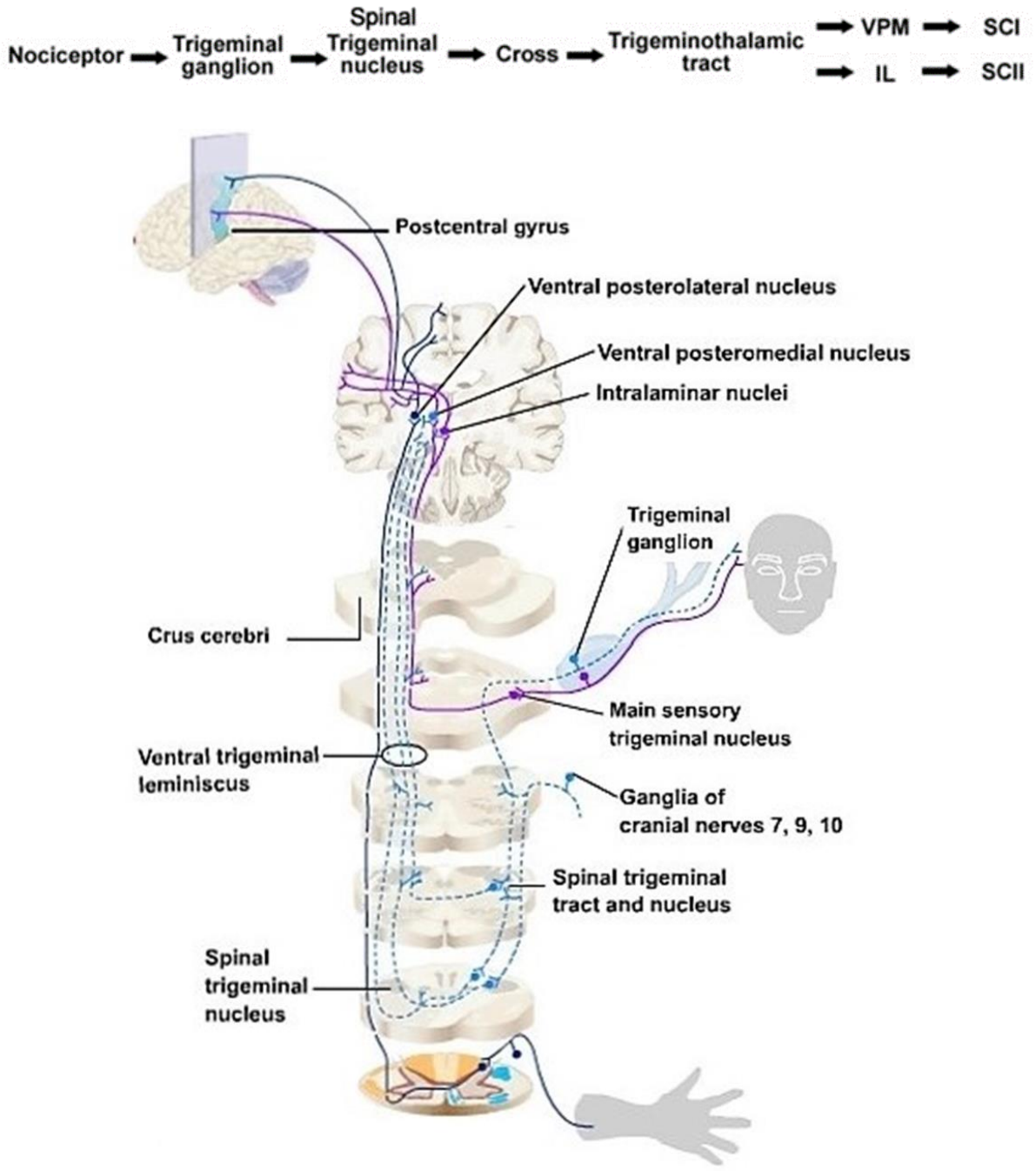


Figure 11 Pain pathways with regard to trigeminal nerve

The **paleospinothalamic tract** is phylogenetically old. The majority of the first-order nociceptive neurons make synaptic connections in Rexed layer II (substantia gelatinosa) and the second-order neurons make synaptic connections in laminae IV-VIII. The second-order neurons also receive input from mechanoreceptors and thermoreceptors. The nerve cells that furnish the paleospinothalamic tract are multireceptive or wide dynamic range nociceptors. Most of their axons cross and ascend in the spinal cord primarily in the anterior region and thus called the ***anterior spinothalamic tract*** (AST).

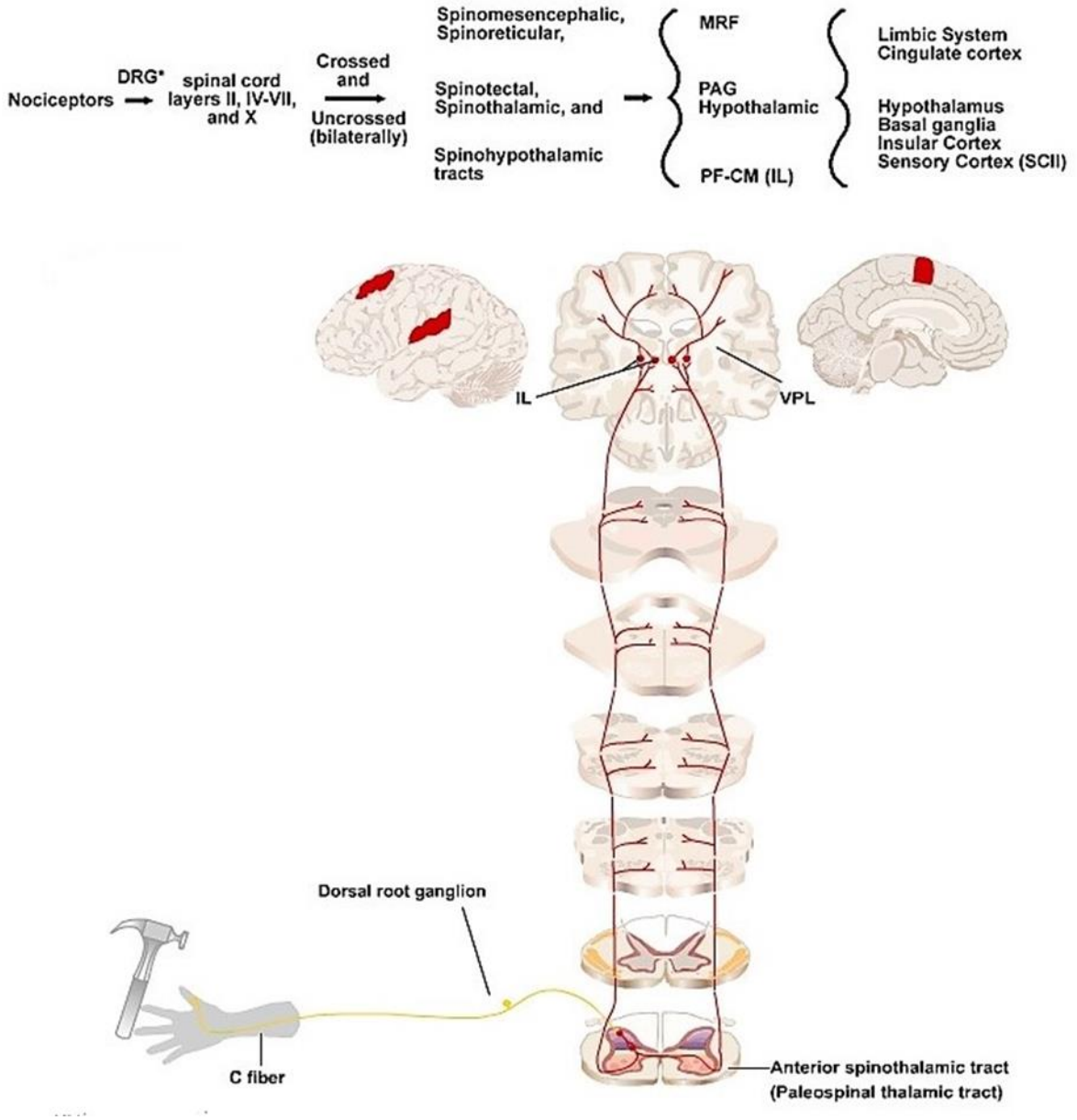


Figure 12 Anterior spinothalamic tract

These fibers contain several tracts. Each of them makes a synaptic connection in different locations:

1. In the mesencephalic reticular formation (MFR) and in the periaqueductal grey (PAG), and they are also called spinoreticular tract;
2. In the tectum, and these fibers are known as the spinotectal or spinomedullary tract; 3) in the PF-CM complex (IL) and they are known as the spinothalamic tract. The above three fibre tracts are known also as the paleospinothalamic tract. The innervation of these three tracts is bilateral because some of the ascending fibers do not cross to the opposite side of the cord. From the PF and CM complex, these fibers synapse bilaterally in the somatosensory cortex (SC II-Brodman area
3. 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.

The multisynaptic tracts which course via the reticular formation also project to the PF-CM (IL) complex. There are extensive connections between the IL and the limbic areas such as the cingulate gyrus and the insular cortex, which is thought to be involved in processing the emotional components of pain. That is to say, the insular cortex integrates the sensory input with the cortical cognitive components to elicit the response to the sensation. The limbic structures, in turn, project to the hypothalamus and initiate visceral responses to pain. That is to say, the insular cortex integrates the sensory input with the cortical cognitive components to elicit the response to the sensation. The limbic structures, in turn, project to the hypothalamus and initiate visceral responses to pain.That is to say, the insular cortex integrates the sensory input with the cortical cognitive components to elicit the response to the sensation. The limbic structures, in turn, project to the hypothalamus and initiate visceral responses to pain.

The intralaminar nuclei also projects to the frontal cortex, which in turn projects to the limbic structures where the emotional response to pain is mediated.

Archispinothalamic Pathway

The **archispinothalamic tract** is a multisynaptic diffuse tract or pathway and is phylogenetically the oldest tract that carries noxious information. The first-order nociceptive neurons make synaptic connections in Rexed layer II (substantia gelatinosa) and ascend to laminae IV to VII. From lamina IV to VII, fibers ascend and descend in the spinal cord via the multisynaptic propriospinal pathway (Figure 7.4) surrounding the grey matter to synapse with cells in the MRF-PAG area. Further multisynaptic diffuse pathways ascend to the intralaminar (IL) areas of the thalamus (i.e., PF-CM complex) and also send collaterals to the hypothalamus and to the

limbic system nuclei. These fibers mediate visceral, emotional and autonomic reactions to pain.

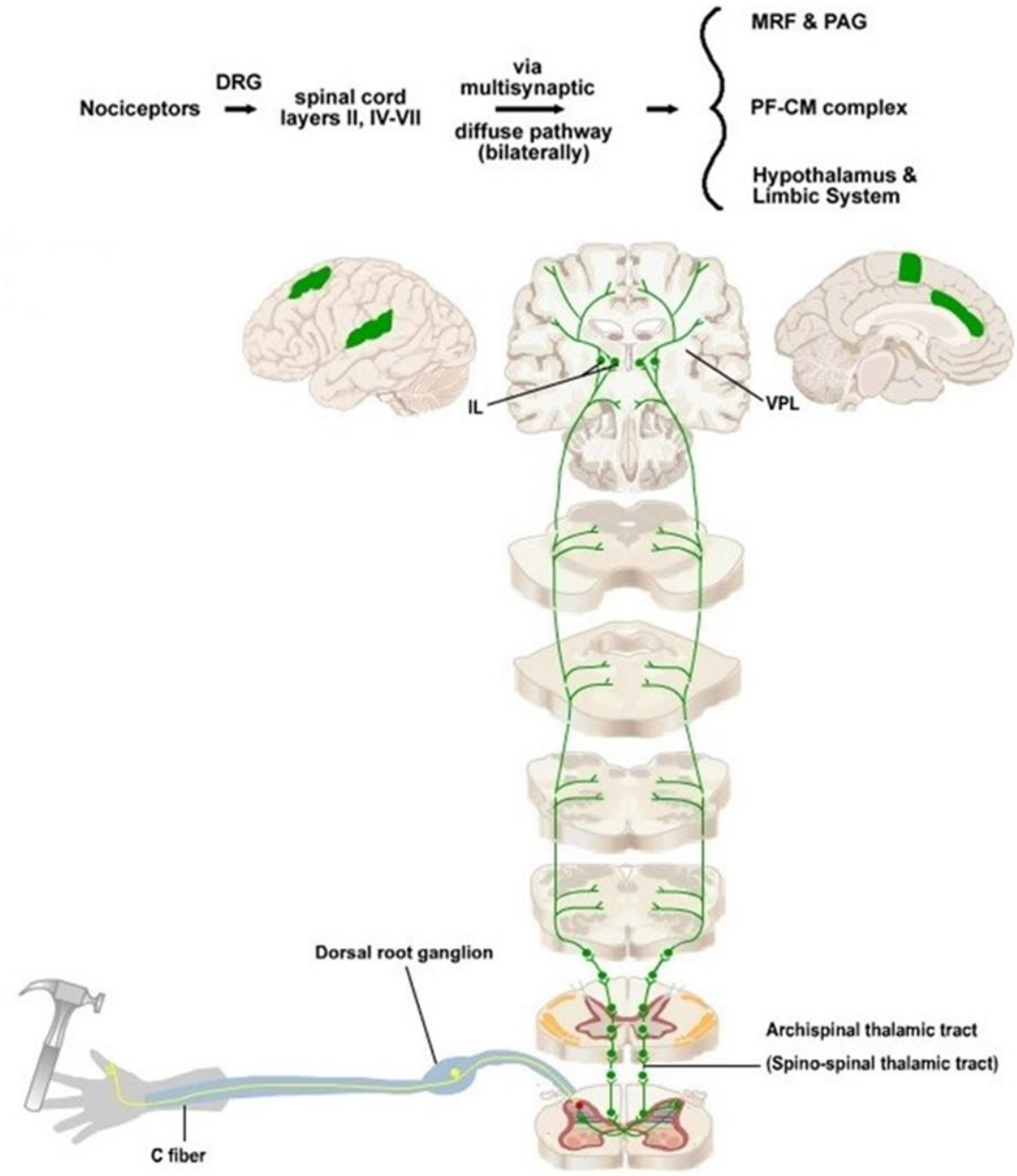


Figure 13 Archispinothalamic pathway

The primary axon, however, remains on the same side of the spinal cord as the side of the body that it innervates (the “ipsilateral” side) until it connects with the second neuron in the chain, which in the case of the lemniscal pathway is located in the medulla. The axon of this second neuron crosses the midline immediately. It then travels up through the medial lemniscus to the ventral posterolateral (VPL) nucleus of the thalamus, where it connects with the third neuron in the chain, travels up

through the medial lemniscus to the ventral posterolateral (VPL) nucleus of the thalamus, where it connects with the third neuron in the chain.

The pathway that carries information about pain and non-painful temperatures is called the neospinothalamic pathway (or often simply the spinothalamic pathway). The first neuron in this pathway connects to the second neuron not in the medulla, but in the dorsal horn of the spinal cord, on the same side that the nerve impulse comes from. This second neuron has a single axon, which immediately crosses the midline to the other (contralateral) side of the spinal cord and goes up to the brain along with the other axons forming the lateral spinothalamic tract. This part of the pathway is described as contralateral, meaning that it runs along the side of the body opposite to the area that its axons innervate.

The last figure (below) summarizes the three major spinal thalamic pathways. Information about bodily events is conveyed by primary sensory fibers to higher brain centres through the dorsal column medial lemniscal pathways. This route is considered a "touch pathway," separate from the spinal thalamic pathways.

However, recent reports indicate that the dorsal column can also carry noxious information from the viscera and widespread skin regions.

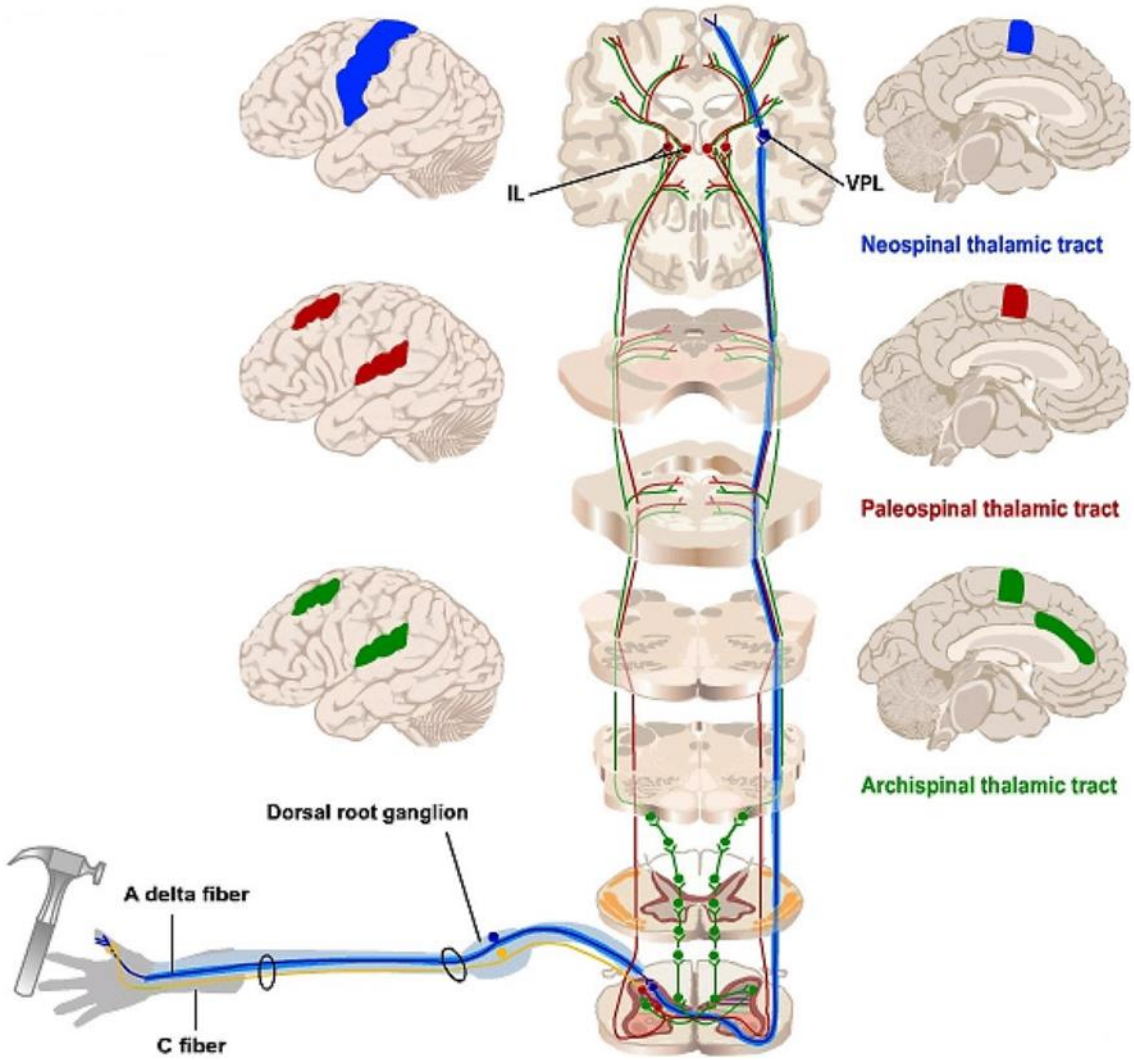


Figure 14 All three pain pathways

The pathway that carries information about **pain and non-painful temperatures** is called the ***neospinothalamic pathway*** (or often simply the ***spinothalamic pathway***). The **first** neuron in this pathway connects to the **second** neuron not in the medulla, but in the dorsal horn of the spinal cord, on the same side that the nerve impulse comes from. This second neuron has a single axon, which immediately crosses the midline to the other (contralateral) side of the spinal cord and goes up to the brain along with the other axons forming the lateral spinothalamic tract. This part

of the pathway is described as contralateral, meaning that it runs along the side of the body opposite to the area that its axons innervate.

The axon of the second neuron connects to the **third** and final neuron of this ascending pathway in the ***ventral posterolateral*** (VPL) nucleus of the thalamus.

In both of these pathways, the third neuron sends its axon to the somatosensory cortex, the part of the brain that determines exactly where the original stimulus occurred in the body.

The difference between the routes of the lemniscal pathway (for touch and proprioception) and the spinothalamic pathway (for pain) have **special clinical significance**, because some injuries that affect only one side of the spinal cord will disrupt only the sense of touch, while others will affect only the sensation of pain.

For example, suppose that the woman in the figure to the right has been injured on the left side of her spinal cord, at the 10th thoracic vertebra. She will experience a reduced sense of touch on the left side of her body below the level of the injury, because the lemniscal pathway runs up the same (ipsilateral) side. She will also experience a reduced sense of pain below the injury, but on the right side of her body, because the spinothalamic pathway runs up the opposite (contralateral) side. As a result of this sensory dissociation, she will be able to feel it when a mosquito lands on her right leg, but not if the mosquito then bites it.

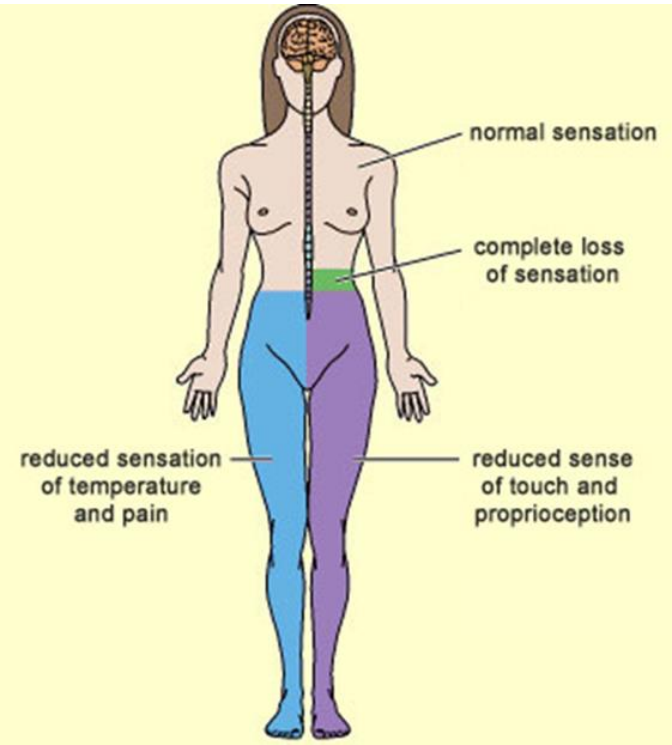


Figure 15 Areas of the body affected by spinal damage

All somatosensory nerve fibres enter the spinal cord via the dorsal horn via the dorsal root ganglion. The subject of neurology doesn't normally go into detail about this ganglion. Here, though, the very thin C-fibres terminate in the most superficial areas of the dorsal horn, but some have connections deeper in the dorsal horn. There they have contact with other neurons, here without any specificity, so there is still a mystery about specific pain pathways. The C - fibres carry information from nociceptors but also temperature sensors. These two go

together right from the beginning of brain processing (*thinks*: *is this a factor why people feel heat in their therapeutic process?).*

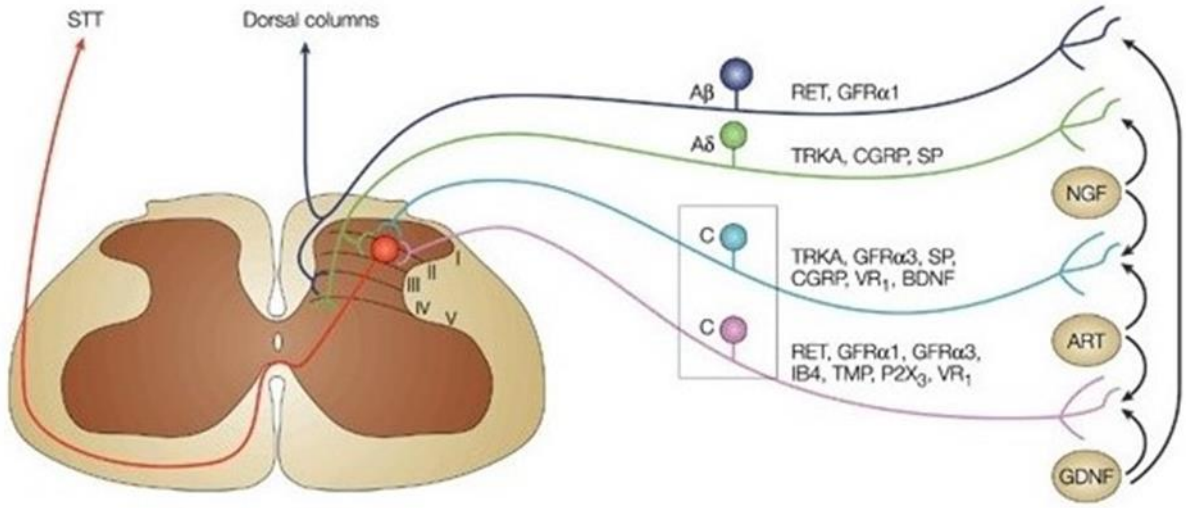


Figure 16 Different nerves and their level of entry into the dorsal horn

There are differences in where different C - fibres terminate dependent upon where they come from in the body: nociceptors in the skin end in an area called the substantia gelatinosa, whereas those from the internal organs, muscles and joints do not. So even though the substantia gelatinosa receives a huge input of these very thin fibres, it is not unique for pain processing.

In any case, then they have synapses with second order neurons. One type of neuron is called the wide dynamic range and are associated with all forms of stimulation: innocuous and painful; these are the largest fibres (so are the fastest) and are connected to larger areas of skin, but also muscles, joints and internal organs. Then there are the nociception specific fibres, however they much fewer in number compared to the wide dynamic range. These appear to injury related and receive input from smaller areas of skin, but also muscles and internal organs.

The second order neurons the pass up sensory pathways in the spinal cord. One route is via the ***anterolateral column*** where it crosses over to the opposite side (contralateral) at the level of sensory input, then passes up on the opposite side of the spinal cord. Another route is via the ***dorsal column***, where it passes up the ipsilateral dorsal column and then decussates at the level of the medulla.

These fibres then pass through the brain stem in the ***periaqueductal grey*** (where those from the dorsal columns can also have relations with the ***reticular formation***) and into the ***thalamus***. From here it passes to the ***sensory region*** of the brain that equates with that part of the body. These are in the parietal region, but also there are also fibres connecting it to the prefrontal cortex via the ***insula*** (located in a deep fold

of the lateral sulcus connecting the frontal, parietal and temporal lobes), which ‘makes sense’ of the experience and then decides what you should to do about it.

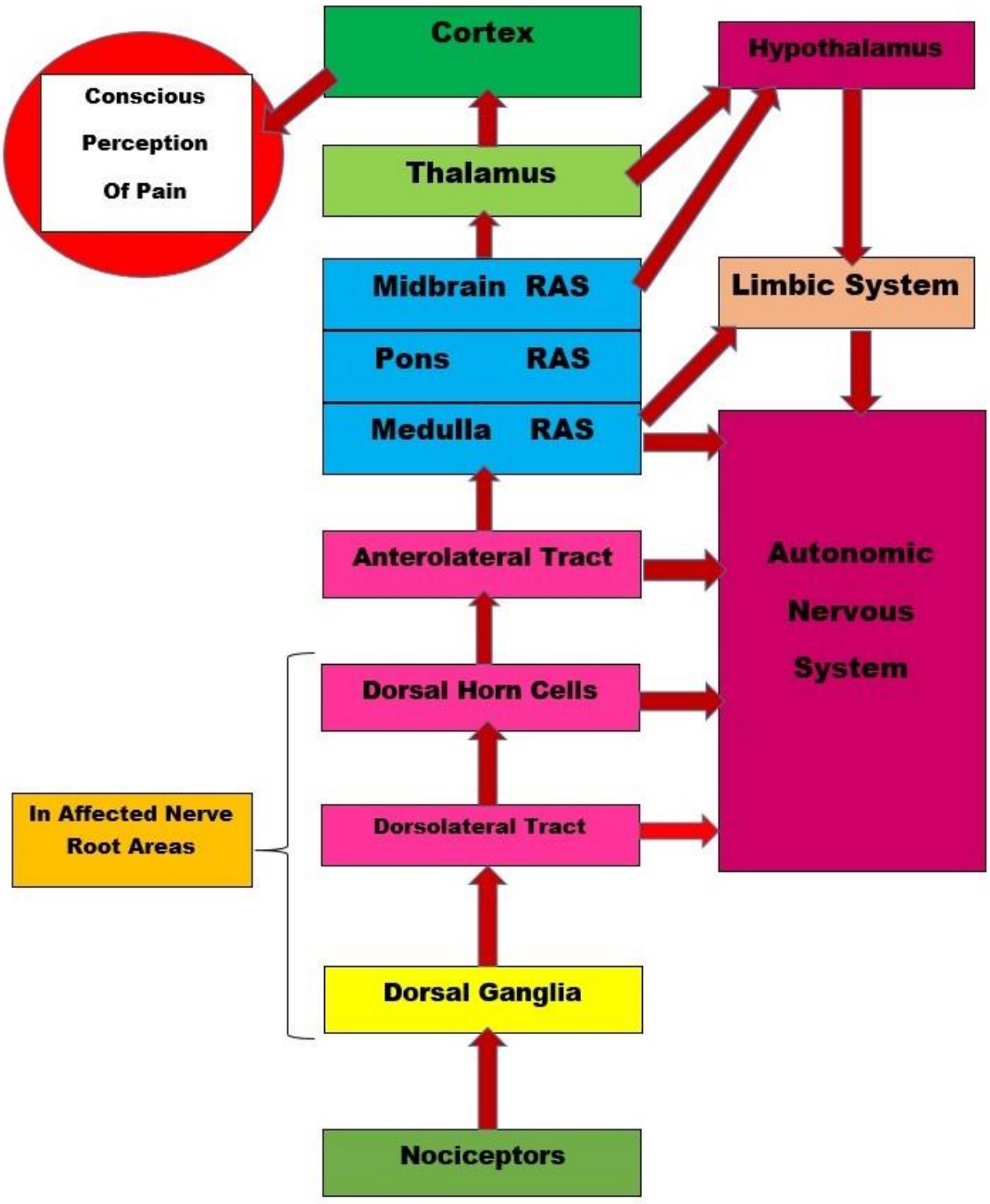


Figure 17 Schematic of pain pathways

Descending Pain-Control pathways

The perception of pain results not simply from the activation of the ascending nociceptive pathways, but from an actual dialogue between these pathways and the various descending pathways that control this pain. The control mechanism

involved is often described as a system of filters or a set of gates whose closing is controlled by the cortex, the midbrain, and the medulla.

But the incoming nociceptive impulse encounters its very first gate as soon as it enters the dorsal root of the spinal cord. This first relay point in the ascending pathway is thus not just an area through which the nociceptive impulse passes, but rather the first place where it is filtered and integrated with other information.

This first level of integration is referred to as **segmental controls of non-pain peripheral origin**. The word “segmental” refers to the fact that this process occurs in each of the segments of the spinal cord corresponding to each vertebra. This segmental control results from the interaction between the nociceptive sensory fibres (A delta and C) and the non-nociceptive ones (A alpha and A beta).

This interaction was modelled in an article, first published in 1962 and then amplified in 1965, which many regard as the most important one ever written on the subject of pain. In this article the authors, Canadian **Ronald Melzack** and Englishman **Patrick Wall**, proposed the first model for the *endogenous control of pain*: the now-famous gate control theory of pain. This theory posits a special form of connectivity involving not only the sensory input fibres for pain and for light touch, as mentioned above, but also a set of inhibitory interneurons that are the key element in the authors’ explanation.

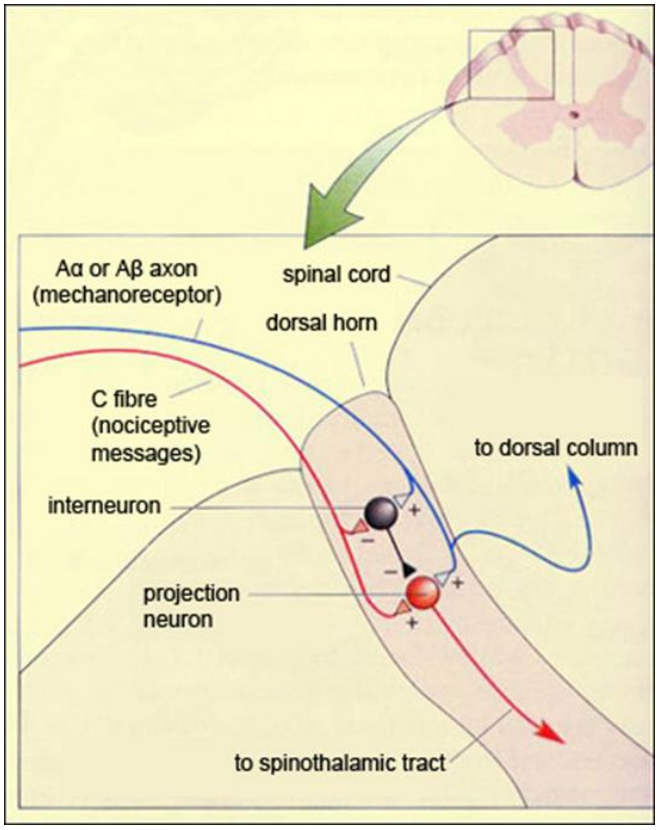


Figure 18 Spontaneous inhibition of pain pathways

As the diagram to the right shows, the nociceptive and non-nociceptive impulses from the body converge at non-specific neurons in the dorsal horn, which project their axons into the contralateral spinothalamic tract. These two types of nerve fibres also communicate with the non-specific neurons through inhibitory interneurons that they contact via collateral fibres. The important difference is the nature of the connection with these interneurons: for the large, non-nociceptive fibres, it is excitatory, but for the nociceptive fibres, it is inhibitory.

It is this particular circuit that forms the virtual gate whose opening and closing will modulate the passage of pain. Under normal conditions, the inhibitory interneurons spontaneously produce action potentials at their own specific frequency. But when the nociceptive fibres are activated by a pain stimulus, in addition to stimulating the non-specific neuron that projects to the spinothalamic pathway (also known as the “projection neuron”), they also inhibit the spontaneous inhibitory activity of the

interneurons, thus depolarizing the projection neuron and increasing the likelihood that it will trigger action potentials.

Another aspect of this circuit's operation is illustrated by what happens when you hurt yourself and start to rub the injured part of your body vigorously. This instinctive reaction reduces the sensation of pain by "closing the gate". But these fibres also make numerous excitatory connections to the inhibitory interneurons. As a result, if you keep rubbing your skin, these interneurons will produce a strong hyperpolarization of the projection neuron, thus greatly reducing the probability that it will emit nerve impulses.

Thus we see how it is the relative frequencies of the action potentials in the nociceptive and non-nociceptive fibres that determine how open the "gate" in the spinal cord will be and hence how much pain information will pass through. In addition, there are projections of central origin that can also activate these inhibitory interneurons in the spinal cord and further close the gate at the segmental level.

Data gathered since 1965 have led to some changes in Melzack and Wall's original model, but the idea that the perception of pain is modulated from the moment that the pain messages enter the spinal cord remains fundamental to the clinical treatment of pain. For example, it is the origin of clinical applications such as transcutaneous electrical nerve stimulation (TENS), which produces local analgesia by stimulating the non-nociceptive fibres in the skin.

Scientists have long known about the phenomenon of **stress-induced analgesia** (SIA), best exemplified by the many reported cases of wounded soldiers and injured athletes who feel no pain while the battle or the game is on, but do feel it afterward, as soon as they are back in conditions of safety and calm.

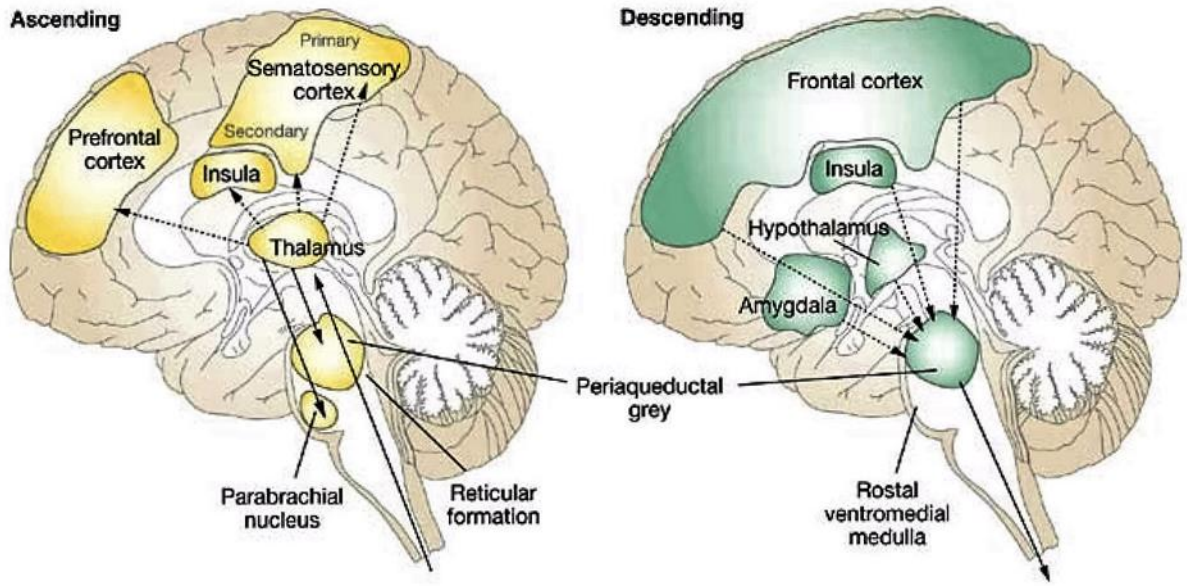


Figure 19 Concept of 'stress induced analgesia'

From an evolutionary standpoint, stress-induced analgesia can be regarded as a component of the fight-or-flight response. It would not be highly adaptive if pain from injuries could prevent us from fighting or fleeing even when our lives depended on it.

But once the threat of death has passed, our normal pain-sensing mechanisms have to do their work in order to immobilize the injured part of the body and prevent the injury from getting worse.

Research done on the mechanisms of the descending control pathways for pain since the early 1980s has now given us a better understanding of stress-induced analgesia. We now know that the tendency to experience this phenomenon varies from one individual to another and is influenced by variables such as age, sex, degree of sensitivity to opiates, and past stressful experiences.

The mechanisms by which stress-induced analgesia inhibits pain seem to involve the descending systems of the midbrain, applying both opioid and non-opioid mechanisms. Research is also tending to show that neurotransmitters associated with stress, such as norepinephrine, and brain structures associated with fear reactions, such as the amygdala, are also involved. Many other endogenous substances, such as anandamide and its cannabinoid receptors, also seem to play a role, in this case in the non-opioid effect in the periaqueductal grey matter.

Pain sensitization

The basic meaning of sensitization is a greater reaction, a lower threshold; an increased reaction to a continuous and constant input. It suggests an enhancement or amplification. We can be sensitized to allergens or politicians. The details of this can be numerous: immunology and neuroscience, cellular and molecular processes as well as behavioural patterns. It can be seen from the increased sensitivity of a single neuron to the enhanced pain perception of a chronic pain patient.

Research into these mechanisms began by looking at the sensitization of peripheral pain receptors from inflammation and the mediators involved (aspirin), to more central pathways in the spinal cord and brain.

There are three crucial processes thought to contribute to pain amplification.

The first of these is the sensitization of peripheral nociceptors. This could be due to direct damage, or the chemicals involved in tissue inflammation. This is also known as *functional pain*. There is an opinion amongst clinicians that irritable bowel syndrome or interstitial cystitis is caused by this, though they have no evidence to prove it.

The second crucial process is the strengthening of synaptic transmission between neurons carrying pain signals in the spinal cord and brain. Synapses are taught to us as fixed structures, but they should be seen as more plastic. It could be seen in terms of the amount of information being transmitted across the synapse, or the change in other modulating neurons present, or even a change in the number or sensitivity of the receptors for the neurotransmitters. Pain hypersensitivity shares mechanistic features with other brain functions, like memory.

The third crucial process is how the brain interprets sensory information. Ideally a light receptor stimulation will be felt as light touch. However, after injury, with

consequent inflammation, such light touch will be felt as pain. Products of tissue injury and inflammation release many compounds.

These produce two separate effects:

- They trigger an inflammatory process aimed at healing the injury
- They change the excitability of the nerve sensors in that region

The chemicals are known in the trade as the *inflammatory soup*. They do not stimulate nociceptors directly, but do contribute to their hypersensitivity and excitability leading to enhanced pain. Normally this situation only lasts as long as the injury. Common anti-inflammatory drugs decrease pain by reducing this inflammation; drugs like the humble aspirin up the more advanced anti-inflammatories all work through this method.

It might be said that all elements in science and medicine revolve around *structures*. Orthodox medicine only sees us in terms of structures: from the big lumps, bumps and tubes, down to the very small ones: cells, molecules and chemicals. Science can see even the smaller ones: the cells, molecules and chemicals. It understands these chemicals as cytokines and neurotransmitters. It explores where they are and what they do there. It has looked at one such chemical called *glutamate*. ***Glutamate*** is a neurotransmitter widespread throughout the brain and spinal cord and it has been found that with this, and its receptors, where two different functions of the brain, pain and memory, crossed.

Memory is a curious, enigmatic, brain function. We may be able to recall events from decades ago, but cannot recall where we put our car keys a little while ago (shared memories can be different again, with members of one family having different memories of the same family event). A crucial aspect of the formation of memories is a prolonged increase in excitability that a persistent input to a neuron called *long term potentiation* (LTP). LTP is also a product of glutamate transmission and similarities have been noticed between areas of the brain related to memory. From this scientists think that pain sensitization is a kind of *pain memory*; where pain perception leaves traces in the brain that contribute to pain sensitivity. Glutamate is involved is this process.

It could also be seen as: if a lot of information goes down a certain route, it facilitates more information going down the same route.

Glutamate is not the only chemical involved in pain sensitization. Another is ***Substance P*** (named Substance Powder, by Ulf von Euler in 1930). It is secreted by neurons and inflammatory cells and acts via the *neurokinin-1 receptor* (NK-1R). (Glucocorticoids (anti-inflammatory steroids) act via decreasing the expression of NK-1R).

Gamma-amino-butyric acid (GABA) is normally one of the most powerful inhibitor neurotransmitters, however during persistent painful stimulation it switches from an inhibitory neurotransmitter and becomes an excitatory one. This means that the same tactile stimulus would now *activate* the pain system, rather than inhibit its

activity. This mechanism is thought to be the cause for the symptoms of touch evoked pain that is characteristic of many chronic pain states.

Now this may all sound very exciting, but it is all information from spinal cord studies. But the brain is where the pain is ultimately 'felt', as the sensation of pain is a brain function.

Frontal lobotomy

Between 1930 and 1960 thousands of people were subjected to frontal lobotomy (or more precisely, prefrontal lobotomy). It involved of a surgical section between the frontal lobes and the rest of the brain. The severing these connections transformed the patients into undemanding people without drives, passion or imagination. It caused a profound change in the cognitive functions of the brain: the ability to understand one's place in the universe (in both space and time) by evaluating the past, assessing the present and planning for the future. They become dull. Lack emotion. They lose will power and are easily distracted. They cannot plan, think things through or make rational judgements or deal with imaginary situations. They are easily satisfied with immediate gratification and do not give any thought to the consequences of their actions. Because of all this, they are easily manipulated and don't cause trouble. Even though they can be euphoric and agitated, eventually they become dull and lifeless. It was used to manage, if not *control*, psychotics, criminal tendencies etc. Antonio Egas (Portuguese) first developed it and won the Nobel Prize in 1949.

In the US, Walter Freeman adopted and performed over 2000 lobotomies, initially on psychotics, then on all sorts of people. The introduction of powerful antipsychotic drugs in the 1950s ultimately lead to its elimination.

Frontal lobotomy, with all this, though, it had an effect on the person's ability to subjectively ***perceive pain***, in that they didn't ***complain about it*** anymore. With all their sensory system being intact, they could still feel pain with all the same stimuli as ordinary people. It was just that feeling pain didn't ***bother*** them anymore. It didn't worry them, or make them unhappy. It had removed the normal link between the ***sensation*** of pain and ***suffering***. Pain had become an event of little consequence because it didn't make them ***suffer***. Through this procedure, medicine found that the overall experienced of pain is one of the highest functions of the brain; cognition.

Cognitive pain

Our experience of pain has three components. We define them individually, but they cannot be seen separately of 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. It 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 affects the regulation to our internal organs (through the autonomic nervous system).

The heart of the emotional element is aversion and '***get rid of my pain'***.

The areas of the brain involved in the emotional reactions to pain are numerous: the **brain stem** (periaqueductal grey), the **hypothalamus** (hormonal regulation through the anterior pituitary), the **amygdala** and the **anterior cingulate nucleus** (just above the corpus collosum). All these, bar the brain stem, are parts of the **limbic system** and are central to our ***emotional experience***. The emotional experience differs though: acute pain states are associated with anxiety, whereas chronic pain generates depressive feelings.

The third component of pain is the **cognitive component** (from the Greek *gnosis* - to know). Here, we not only feel pain and show an aversive reaction to it but also, we worry about its ***meaning*** in our life; why do I feel the pain? What will it mean to my survival and my future? How will it affect my life and of the lives of those people around me? Will it go away soon and how will it influence my life, my work and my social life? Will I be able to go back to the gym again, or go join my hill-walking friends? Is it serious and am I going to die?

These cognitive functions are all **frontal lobe** functions. This also has lots of connections with the limbic system. Here cognition, with regard to pain, requires self-consciousness and it is here that pain cognition becomes a uniquely human experience. Cognitive pain is what transform pain in to suffering. Can you have an unpleasant reaction to pain and yet not worry about what it means for your survival? A frontal lobotomy will achieve this, though drugs, especially the opiates, also disassociate the sensory from the cognitive brain.

Thus all pain, in the end, is in the brain. Humans deem themselves to be the highest in the evolution of animals and, as part of this, pain has evolved into ***suffering***; one of the highest and most complex functions of the human brain.

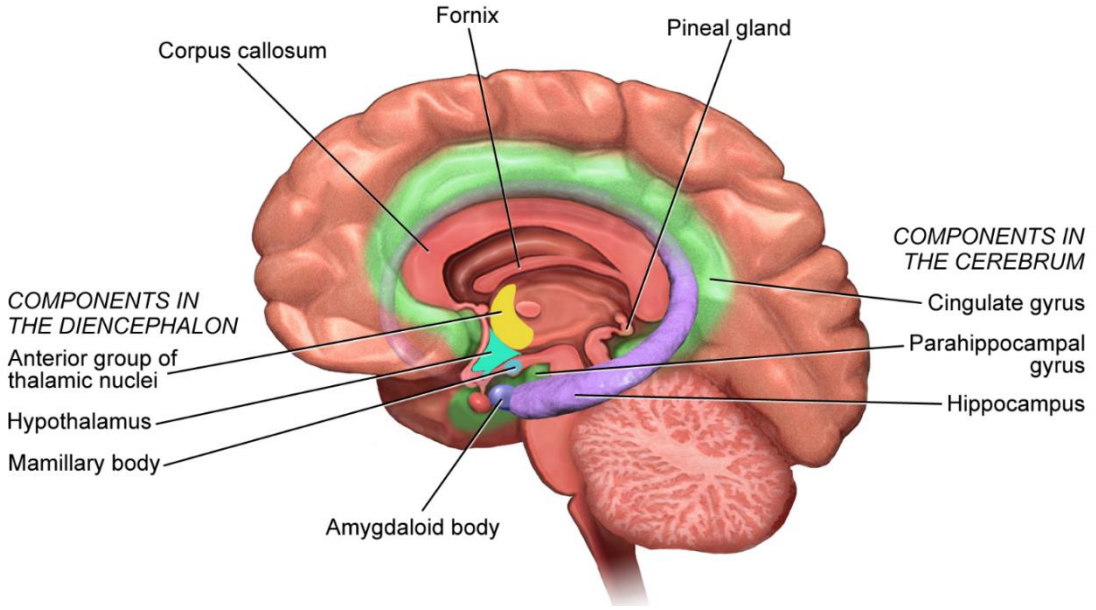


Figure 20 The limbic system

Brain imaging studies of pain have generated two important pieces of knowledge:

- Many regions of the brain are stimulated simultaneously during a painful experience, and
- Chronic pain literally changes the structure of your brain

A brief painful stimulus will activate the **somatosensory cortex** in the posterior part of the brain); this is feeling the pain. However two other centres are activated in the anterior part of the brain:

- **Insular cortex**. This region was once just associated with the processing of sensations from internal organs, and other complex ones like orgasm or tiredness. However it has also been to active during emotional and affective feelings, like motherly love or craving certain foods
- **Anterior cingulate cortex**. This is active during emotional events, but particularly if the association is negative. It is involved in the unpleasantness and aversion of the painful experience.

These areas integrate the emotional component of the pain experience and provide a link between the emotional and the cognitive elements of pain perception. This is curious, it might be said, as we presume we have a degree of self-awareness. A rat would only need one experience of pain and it would not 'go there again' (I was walking my dog one day and he put his nose to an electrified fence. He let out a loud yelp. He never went near that fence ever

again, even if I tempted him with treats). A human could take a lifetime to ‘learn’; and we presume that we ‘know ourselves’.

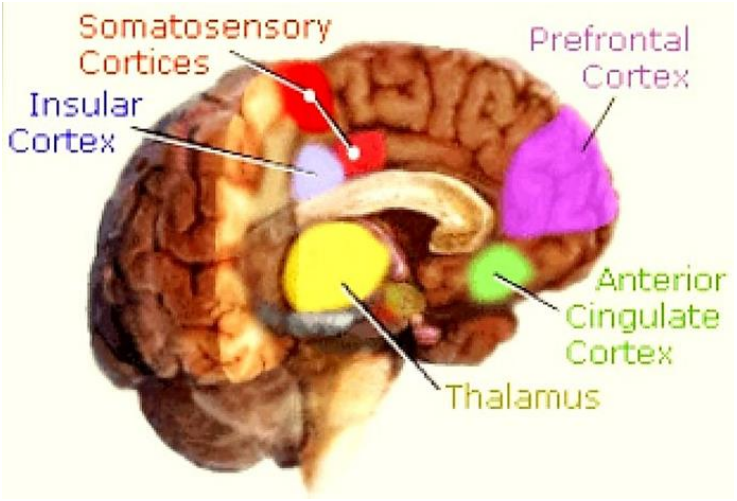


Figure 21 Insular cortex and anterior cingulate cortex

Brain scans of chronic pain patients are different, in that there are changes in in the intensity of activation of brain regions and abnormal activation of some brain areas. Interestingly, each abnormality is related to a specific chronic pain disease. Such changes was first seen in people who had chronic low back pain. They showed a reduction in the grey matter in the **thalamus** (a sensory processing station) and a reduction in the grey matter of the **prefrontal cortex** (relating to the cognitive and emotional aspects of the pain). This alteration of brain matter is mirrored in other chronic pain states; a reduction of the grey matter in those areas activated by pain, particularly in those that integrate emotional and cognitive elements. Along with this, changes have been found in the pathways of neurons of serotonin (5HT) and dopamine; two neurotransmitter involved in *reward* responses.

So, are these changes the result of the chronic pain, or the consequence of it?

We don’t know the answer to the first question. With regards to the second, chronic pain **is** associated with psychiatric conditions (depression and chronic anxiety), and people with chronic pain **do** show cognitive impairment. It has been noted that chronic pain enhances the need for short-term reward - immediate pain relief - at any cost and mitigates against the more logical choice of a long-term reward.

Sources of Pain

Somatic Pain

Somatic pain can be classified as either:

1) Cutaneous, superficial or peripheral pain and
2) Deep pain.

1. ***Cutaneous, Superficial or Peripheral Pain***. Pain that arises from the skin and muscles or peripheral nerves themselves. In general, this pain has two

components, the initial response (a) followed by later response (b). These signals are transmitted via different pathway.

A. Pricking pain reaches the CNS via ***neospinothalamic tract*** (i.e., LST) to the VPL (or VPM) and to the SCI.

B. Burning and soreness pain resulting from tissue damage reaches the CNS via the paleospinothalamic tract (AST) and archispinothalamic tract to brain stem nuclei and to PF-CM complex, etc.

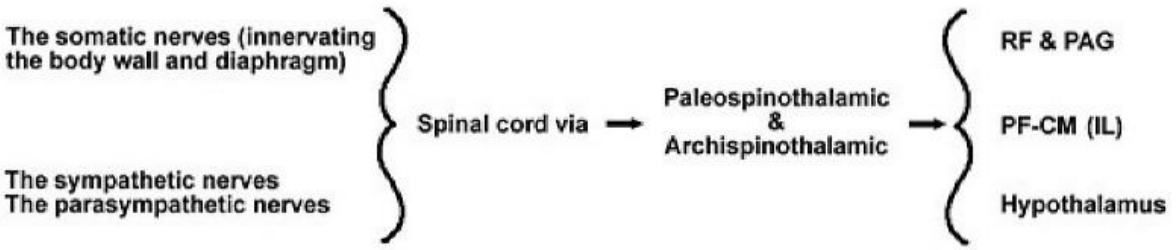
2. ***Deep pain***. This pain arises from joint receptors tendons and fascia (i.e., deep structures). The quality of deep pain is dull, aching or burning. Deep pain is accompanied by a definite autonomic response associated with sweating and nausea, changes in blood pressure and heart rate. Somatic deep pain reaches the CNS mainly via the paleospinothalamic and archispinothalamic tract.

Reaction to Somatic Pain. Sudden, unexpected damage to the skin is followed by three responses:

A. ***Startle response***. This is a complex psychosomatic response to a sudden unexpected stimulus which includes: A flexion reflex, postural readjustment and orientation of the head and eyes to examine the damaged area.
B. ***Autonomic response***. This response includes: NE and E release, ACTH and/or cortisol release, and vasoconstriction and piloerection.
C. ***Behavioural response***. This response includes: Vocalization, rubbing designed to diminish pain, learning to respond to sudden pain and psychosomatic pain.

Visceral Pain

In the visceral organs, 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. It conveys also hunger, thirst, electrolyte balance, irregulation in the respiratory and circulatory

systems. Many of these signals reach the CNS bilaterally by the following three channels:

In the visceral organs, free nerve endings are scattered, and any stimulus that excites these nerve endings causes visceral pain. Such stimuli include spasm of the smooth muscle in a hollow viscus, or distention or stretching of the 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 as a result of gastrointestinal lesions, and tumours as well as thrombosis of an artery. In many cases, visceral pain is not localized to the site of its cause, rather in a distant site.

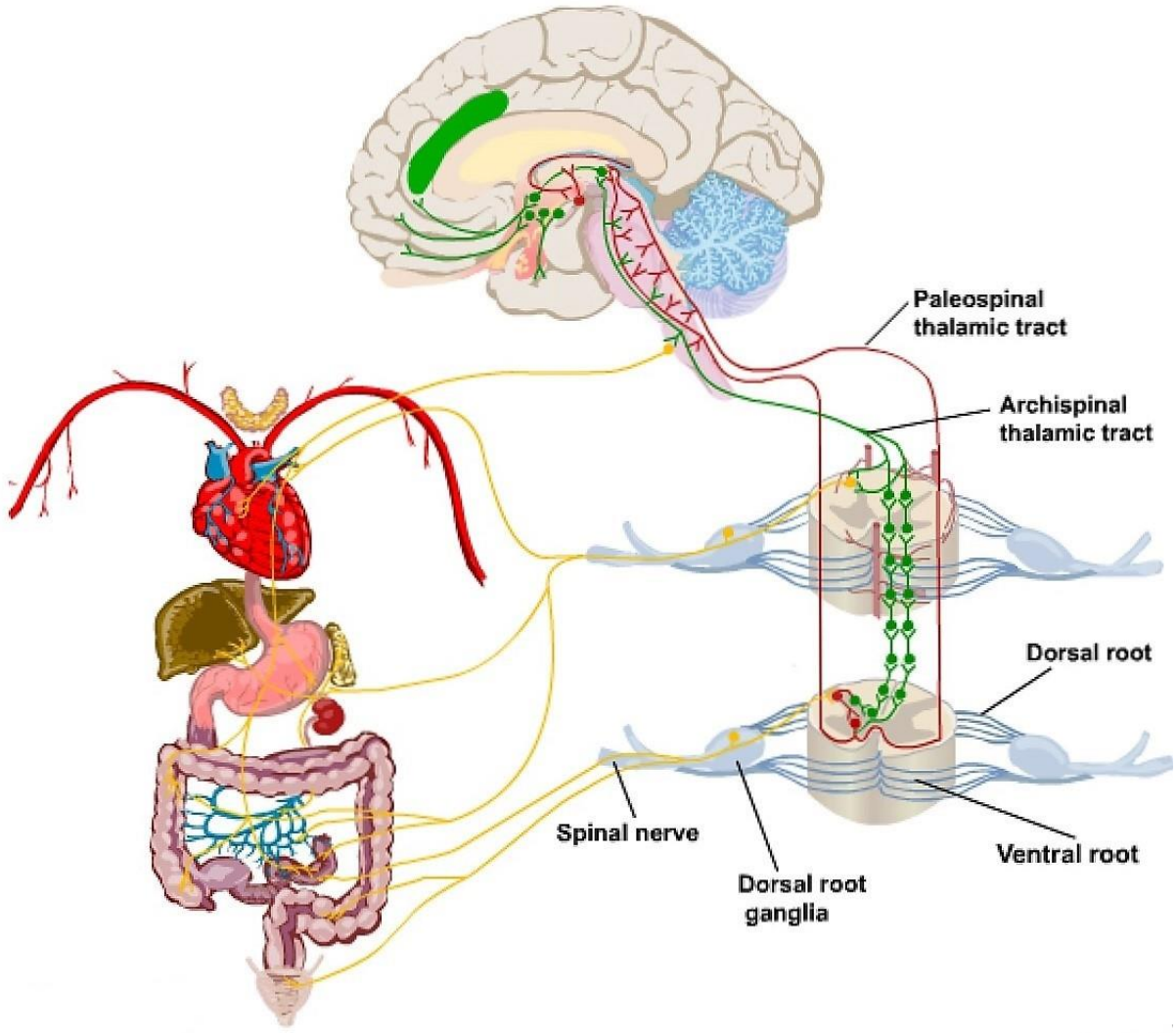


Figure 22 Neural pathways carrying pain information from visceral organs

Thalamic Pain

Stroke or occlusion in the thalamogeniculate artery (a branch of the posterior cerebral 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 as well as local manifestations of diencephalic lesions 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.

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.** The 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. 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 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).

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 localized to a

distant site. One possible exception is that the axons carry pain information from the viscera enter into the spinal cord by the same route as the cutaneous pain sensation axons. Within the spinal cord there is a convergence of the information on the same nocineurons. This convergence gives rise to the phenomenon of referred pain. For example, pain associated with angina pectoris, or myocardial infarction is referred to the left chest, left shoulder, and upper left arm. Pain resulting from distention of the colon is referred to the periumbilical area.

The following are some hypothesis to explain referred pain

1. 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 3-5).

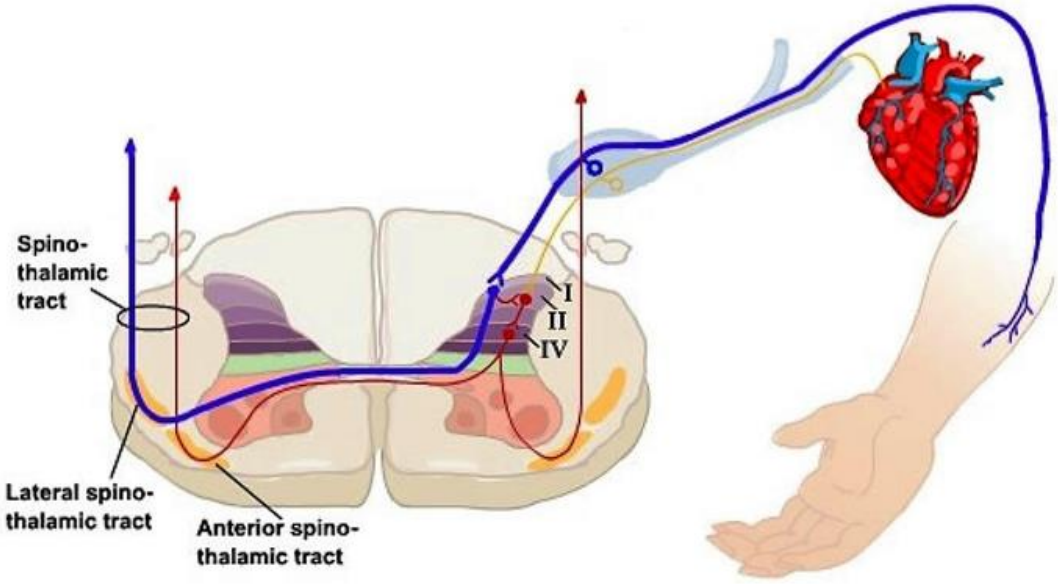


Figure 23 Convergence in referred pain is carried by the paleospinothalamic tract

2. 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.
3. 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 centres and the brain interprets the pain as being from the skin.

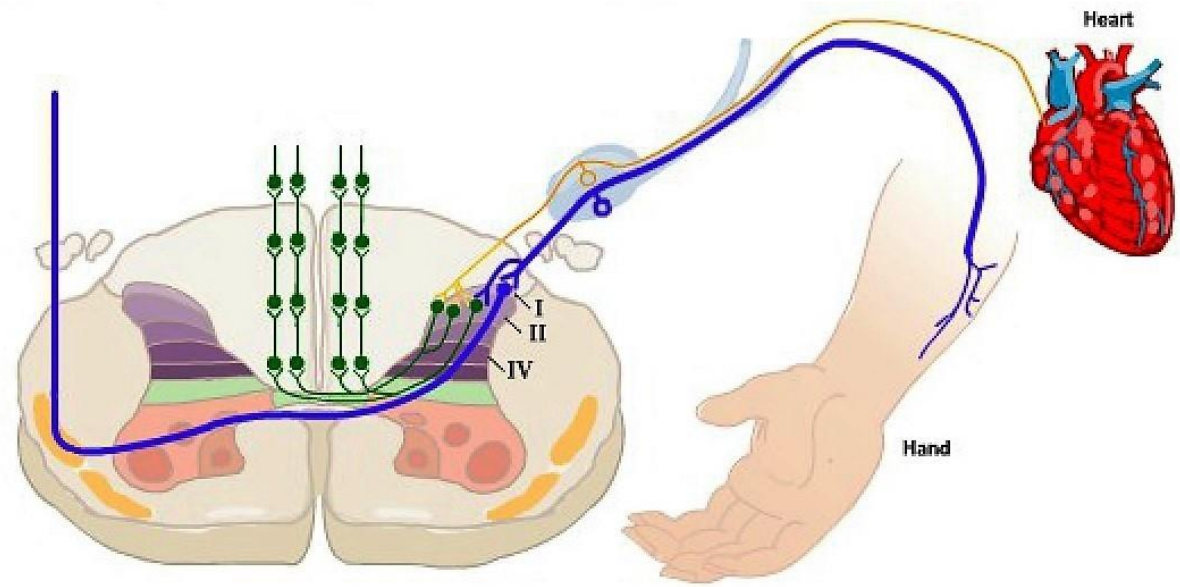


Figure 24 Convergence of referred pain

4. Learned phenomenon. Visceral information arrives in the CNS. However, the brain interprets that the impulses originate from the site of a previous surgical operation, trauma or localized pathologic process.

Table 2 Tables of referred pain

The table shows the relations between the cutaneous areas and the internal organs	
Areas in the trunk and limbs	**Areas in the head**
Heart C3, C4 – D2 – D8	**Ventricles and aorta N, FN, MO, FT** **Auricles FT, T, V, P,**
Lungs C3, C4 – D4 – D9	**N, FN, MO, FT, T, V, P**
Stomach D7 – D9	**FN, MO, T, V, P**
Intestine D9 – D12	**V, P, O**
Rectum Sac2. Sac 3. Sac4	**FN, MO, T, V, P, O**
Liver C3, C4 – D7 – D10	**T, V**
Gall bladder D8 – D9	
Kidneys and urethra D11 – L1	
Bladder (mucous membrane and neck) Sac3. Sac4	
Detrusor vesicae D11 – L2	
Prostate D10 – D12, Sac1. Sac3	
Epididymis D11 – D12	
Testicle D10	**O**
Ovary D10	**O**
Ovarian appendage D11 – L1	
Uterus D10 – L1	
Neck of uterus Sac2. Sac4	
Mammae D4 – D5	
Spleen (from Signorelli) D6	
The areas of the head are indicated as follows	
N - Nasal or rostral area; FN - Fronto-nasal area; MO - Medio-orbital area; FT - Fronto-temporal area; O - Occipital area; T - temporal area; V - Vertical area; P - Parietal area; NL - Nasolabial area; Max = Maxillary area; Man - Mandibular area; Men - Mental area; Ls - Superior laryngeal area; LI - Inferior laryngeal area; To - Hyoid area	

<table>
<tr><td>Large Intestine
Acute or chronic low back pain
Sciatica left (venous circulation problems)
Sciatica right (caecum)
Varicose veins - left
Joint pains in lower limbs
Glenohumeral arthritis</td><td rowspan="2">Liver
C4-5 right or bilateral
Right scapula
Right glenohumeral joint
Cervical / brachial plexus and fascia
Cranial base restriction on right
Sciatica left (venous hepatic origin)
Sciatica right (related to hepatic fascia, right kidney, ascending colon)</td></tr>
<tr><td>Duodenum
T 12 - L1 (right > left)</td></tr>
<tr><td>Gallbladder
C 4-6 right
C4 transverse process
T 7-9 right costovertebral joint</td><td rowspan="2">Female reproductive system
T4 - 5 Breasts
T10 - Ovaries
T11 - L1 Ovarian appendage
T10 - L1 Uterus
S2; S4 Neck of Uterus
Lumbosacral - urogenital problems
Knee - genitocrural nerve
C 2-4 Hormone problems (via hypothalamic pituitary axis)</td></tr>
<tr><td>Lungs
Liver, stomach, oesophagus, sternum, costal cartilage
Rib 1 - stellate ganglion
Cervical spine</td></tr>
<tr><td>Bladder
L 2-3 associated with incontinence
Sacrococcygeal - associated with feet</td><td>Kidneys
T 6-7
T 10 - 12 costovertebral
Flank pain radiating into groin
Inferior navicular (K2 acupuncture point)</td></tr>
</table>

Phantom (illusory) Pain

Phantom 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:

1) From 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.

Acute Pain

Acute pain arises from activation of nociceptors for a limited time and is not associated with significant tissue damage (e.g., a pin prick).

Chronic Pain

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

Sensitization

One possible explanation for chronic pain is a phenomenon called **sensitization**. Following continuation and prolong noxious stimulation, nearby silent nociceptive neurons that previously were unresponsive to stimulation, now 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 cause 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. 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 centres in the brain. This phenomena 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 stimulate 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 on nociceptive dorsal horn cells, this constant glutamate release via G protein dependant phosphorylation cascades results in opening of postsynaptic ion channels gated by the NMDA receptors. This

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.

Fibromyalgia

Fibromyalgia is characterized by widespread chronic pain throughout the body, including fatigue, anxiety and depression. It is now believed that it has a genetic component which tends to run in families.

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
- Haemorrhage (parenchymal and subarachnoid)
- Trauma
- Withdrawal syndromes
- Severe hypertension
- Dental, cranial vault, TMJ, and myofascial disorders
- Cervical spine and occipitocervical junction disorders

Summary

Because of the importance of warning signals of dangerous circumstances, several nociception pathways are involved to transmitting these signals and some of them are redundant.

The neospinothalamic tract conducts fast pain (via Aδ fibers) and provides information of the exact location of the noxious stimulus, and the multisynaptic paleospinothalamic and archispinothalamic tracts conduct slow pain (via C fibers), a pain which is poorly localized in nature (see Figure 14).

Pain activates many brain areas, which link sensation, perception, emotion, memory and motor reaction. Therefore, many pain clinics target their treatments to block the perception of pain using psychosomatic means of treatments such as biofeedback,

hypnosis, physical therapy, electrical stimulation, and acupuncture-multimodal treatment.

Pain medication

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.

Uses

These drugs provide pain management.

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

Broadly speaking, anagesics can work centrally or peripherally:

Site of action	Drug
Peripheral	NSAIDS Local anaesthetics Opioids
Central nervous system	Opioids Antidepressants Anticonvulsants Paracetamol Local anaesthetics

Figure 25 Sites of action typical analgesics

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 two and four hours. Paracetamol is classified as a mild analgesic. Paracetamol is generally safe at recommended doses.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) - general list

Generic	Brand Name
Diclofenac	*Cataflam, Difene, Voltarol, Diclac*
Etodolac	*Lodine, Eccoxolac, Etopan*
Fenoprofen	*Fenopron*
Flurbiprofen	*Fropen*
Ibuprofen	*Neurofen, Buplex, Cramp End, Provin*
Indomethacin	*Indocid, Indocin SR, Tivorbex*
Ketoprofen	*Ketocid, Ketovail, Orudis, Oruvail, Powergel, Tiloket*
Ketorolac	*Trometamol*
Meclofenamate	*Meclomen*
Mefenamic Acid	*Ponstan*
Meloxicam	
Nabumetone	*Relafen*
Naproxen	*Aleve, Anaprox, Naprosyn*
Anaprox DS,	*EC-Naprosyn, Naprelan, Naprosyn*
Piroxicam	*Brexidol, Feldene, Feldene Melt*

NSAIDs

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs), function through inhibition of ***cyclooxygense-1***, reducing the production of *prostaglandins* and other inflammatory cytokines. They are a drug class that groups together drugs that provide analgesic (pain-killing) 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.

COX-2 Inhibitors

Generic	Brand Name
Etoricoxib	*Arcoxia*
Celecoxib	*Celebrex*
Diclofenac	*Cataflam, Difene, Voltarol, Diclac*
Paracoxib	*Dynastat*

COX-2 inhibitors

These drugs have been derived from NSAIDs. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least 2 different versions: COX1 and

COX2. Research suggested most of the adverse effects of NSAIDs to be mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX2 (inducible) enzyme. Thus, the COX2 inhibitors were developed to inhibit only the COX2 enzyme (traditional NSAIDs block both versions in general). These drugs (such as ***rofecoxib, celecoxib, and etoricoxib***) are equally effective analgesics when compared with NSAIDs, but cause less gastrointestinal haemorrhage in particular.

After widespread adoption of the COX-2 inhibitors, it was discovered that most of the drugs in this class increase the risk of cardiovascular events by 40% on average. This led to the withdrawal of *rofecoxib* and *valdecoxib*, and warnings on others. *Etoricoxib* seems relatively safe, with the risk of thrombotic events similar to that of non-coxib NSAID *diclofenac.*

Narcotic Pain Medications (Painkillers)

Generic	Brand Name
Buprenorphine	*Buprenex, Butrans transdermal patch*
Butorphanol	*Stadol*
Codeine	
Hydromorphone	*Dilaudid, Dilaudid-5, Dilaudid-HP, Hydrostat IR, Exalgo ER*
Ixprim	*Tramadol*
Meperidine	*Pethidine*
Morphine	*Oramorph; Sevredol; Filnarine; Morphgesic; MST Continus MXL; Zomorph*
Nalbuphine	*Nubain*
Oxycodone	*OxyContin, Roxicodone, Oxecta, Oxynorm*
Oxymorphone	*Numorphan*
Pentazocine	*Talwin*
Propoxyphene	*Cotanal-65, Darvon*
Tapentadol	*Nucynta*

Opioids

Morphine, the archetypal opioid, and other opioids (e.g., *codeine, oxycodone, hydrocodone, dihydromorphine, pethidine*) all exert a similar influence on the *cerebral opioid receptor system*. *Buprenorphine* is a partial agonist of the μ-opioid receptor, and *tramadol* is a *serotonin norepinephrine reuptake inhibitor* (SNRI) with weak μ-opioid receptor agonist properties. *Tramadol* is structurally closer to *venlafaxine* than to *codeine* and delivers analgesia by not only delivering "opioid-like" effects (through mild agonism of the mu receptor) but also by acting as a weak but fast-acting serotonin releasing agent and norepinephrine reuptake inhibitor. *Tapentadol*, with some structural similarities to *tramadol*, presents what is believed to be a novel drug working through two (and possibly three) different modes of action in the fashion of both a traditional opioid and as a SNRI. The effects of serotonin and norepinephrine on pain, while not completely understood, have had causal links established and drugs in the SNRI class are commonly used in conjunction with opioids (especially *Tapentadol* and *tramadol*) with greater success in pain relief. Dosing of all opioids may be limited by opioid toxicity (confusion, respiratory

depression, myoclonic jerks and pinpoint pupils), seizures (tramadol), but opioid-tolerant individuals usually have higher dose ceilings than patients without tolerance.

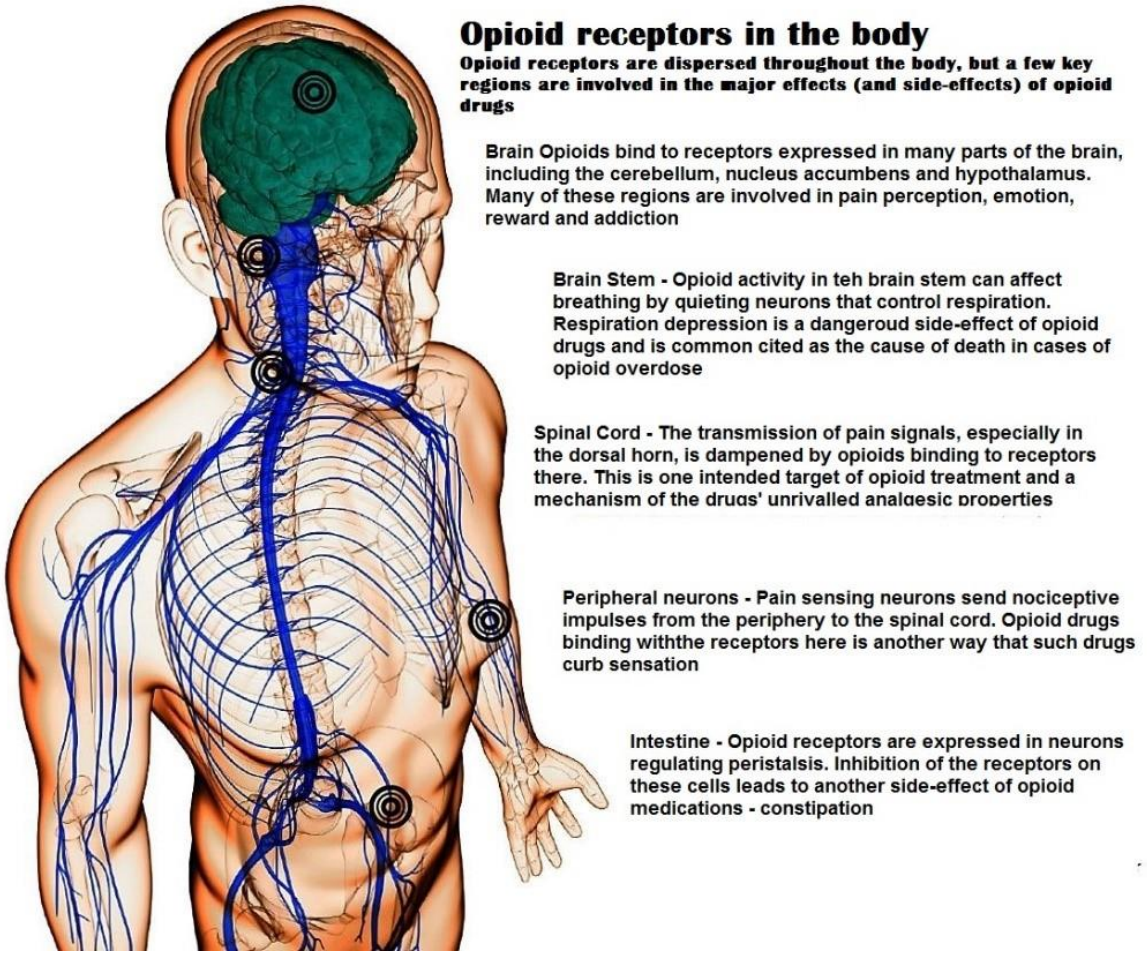


Figure 26 Distribution of Opiate receptors throughout body

Opioids, while very effective analgesics, may have some unpleasant side-effects. Patients starting morphine may experience nausea and vomiting (generally relieved by a short course of antiemetics such as *Phenergan*). Pruritus (itching) may require switching to a different opioid. Constipation occurs in almost all patients on opioids, and laxatives (lactulose, macrogol-containing or co-danthramer) are typically co-prescribed.

When used appropriately, opioids and other central analgesics are otherwise safe and effective, however risks such as addiction and the body's becoming used to the drug (tolerance) can occur. The effect of tolerance means that frequent use of the drug may result in its diminished effect so, when safe to do so, the dosage may need to be increased to maintain effectiveness. This may be of particular concern regarding patients suffering with chronic pain.[citation needed] Opioid tolerance is often addressed with "opioid rotation therapy" in which a patient is routinely switched between two or more non-cross-tolerant opioid medications in order to prevent exceeding safe dosages in the attempt to achieve an adequate analgesic effect.

Central Analgesics

Generic	Brand Name
Tramadol	*Ultram, Zydol*
Tramadol and Paracetamol	*Ultracet, Tramacet*

GABA (neuromodulators)

Generic	Brand Name
GABA	*Lyrica, Neurontin, Neurostil*

GABA analogues mainly function through altering (modulating - reducing) nerve (synaptic) transmission

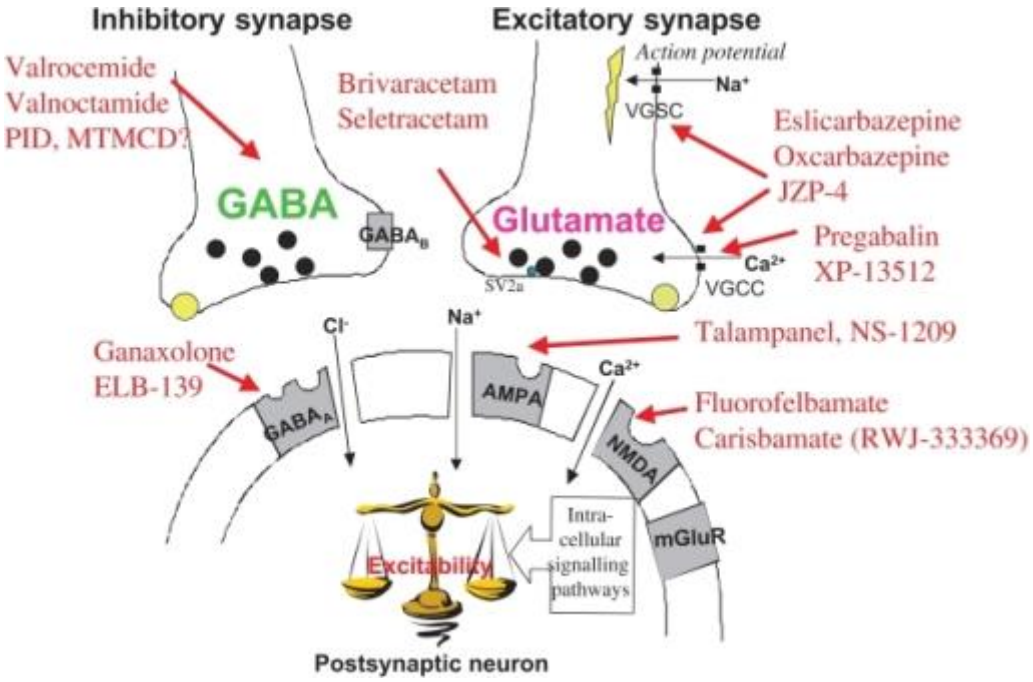


Figure 27 Action of GABA analogues

Adrenergic Alpha (2) receptor agonists

Generic	Brand
Clonidine	*Catapres*

In recent years, alpha (α2) agonists have found wider application, particularly in the fields of anaesthesia and pain management. 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.

The α2 agonists that are currently employed include *clonidine.* α2 Adrenergic receptors are present in both presynaptic and postsynaptic neurons in the central and peripheral nervous system. Activation of presynaptic receptors results in the propagation of negative feedback loop inhibiting the release of norepinephrine.

Activation of postsynaptic receptors in the central nervous system inhibits sympathetic activity.
At supraspinal level, α2 adrenoceptors are present in high concentrations at the locus coeruleus in the brainstem. It is the origin of the medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. At the spinal level, stimulation of α2 receptors in the substantia gelatinosa in the dorsal horn results in the inhibition of nociceptive neurons and in the release of substance P.

Combinations

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

Narcotic Analgesics and Aspirin

Generic	Brand Name
Aspirin, Caffeine, and Dihydrocodeine	*Synalgos-DC*
Aspirin and Codeine	*Empirin with Codeine*
Hydrocodone and Aspirin	*Damason-P, Lortab ASA, Panasal 5/500*
Migraleve	*Codeine Phosphate, Paracetamol DC, Buclizine Hydrochloride*
Solpadeine	*Paracetamol, Caffeine, Codeine Phosphate Hemihydrate*

Combinations
Analgesics are frequently used in combination, such as the paracetamol and codeine preparations found in many non-prescription pain relievers. 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.

Topical Analgesics

Generic	Brand Name
Capsaicin	*ArthriCare, ARTH-RX, Axsain, Capsagel, Dura-Patch, Methacin, Qutenza,*	*Zotrix, Zotrix-HP*

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.

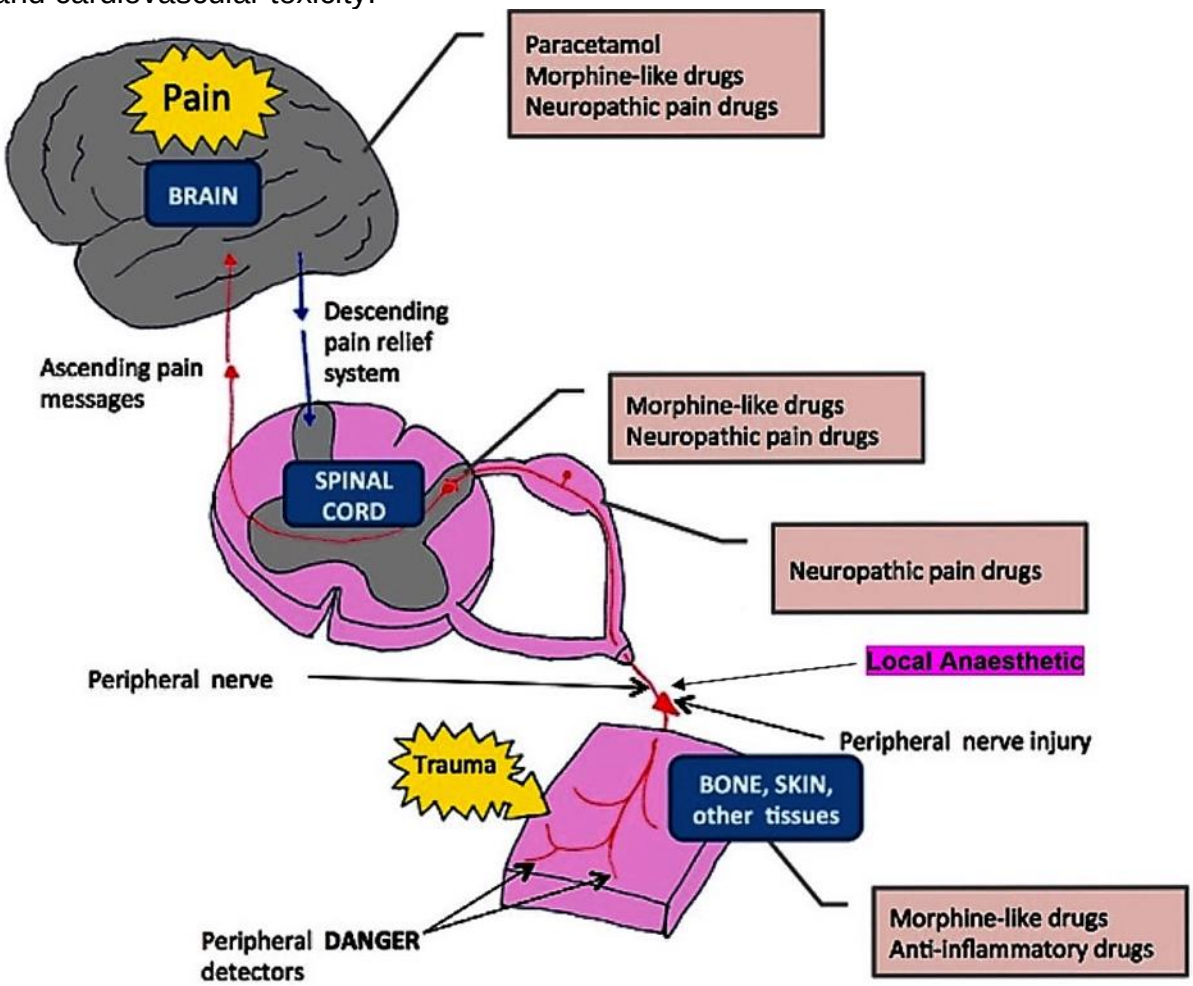


Figure 28 Actions of analgesics

Topical Anesthetics

Generic	Brand Name
Benzocaine	*Benzocaine, Tyrothricin*
Benzocaine / Menthol	*Benzocol, Butyl Aminobenzoate, Dermoplast*
Dibucaine	*Cinchocaine, Nupercainal Cream, Nupercainal Oinment*
Lidocaine	*LidaMantle, Lidoderm, Lignocainem, Xylocaine*
Lidocaine/ Prilocaine	*EMLA*

Antidepressants for neuropathic pain

Tricyclic antidepressants

Brand	Generic
Amitriptyline	*Lentizol, Tryptizol, Domical, Elavil*

Selective Serotonin/nor-adrenalin reuptake inhibitors (SNRI)

Brand	Generic
Duloxetine	*Cimbalta, Yentreve*
Venlafaxine	*Efexor,*

Antidepressants including tricyclics (e.g. ***amitriptyline****)* and serotonin / noradrenaline reuptake inhibitors (e.g. ***duloxetine, Venlafaxine***) are used to treat neuropathic pain. They increase the concentration of serotonin and noradrenaline in the CNS, facilitating the descending inhibitory serotonergic and noradrenergic pathways.

Anticonvulsants

Anticonvulsants such as ***gabapentin*** (GABA analolgue) and ***carbamazepine*** (Tegretol) are also used for neuropathic pain. They inhibit the release of excitatory neurotransmitters and therefore pain transmission.

Multimodal analgesia

Multimodal analgesia describes using a combination of drugs with different modes of action. In this way it may be possible to use lower doses of drugs, minimising unwanted side effects. For example, by using a combination of NSAID-opioid and opiod-α2 agonist drugs for postoperative pain, the amount of opioid required is less and opioid related side effects are reduced.