

# An introduction to pain pathways

By the perioperativeCPD team

## Introduction

Pain plays an important role in the survival of all animals. Its purpose is to act as a signal, alerting us to potential damage, and leads to a range of actions to prevent or limit further damage.

The pain 'system' comprises a number of elements that detect the noxious stimulus, convert it to a nerve impulse and transfer that impulse rapidly up the spine through the brainstem and finally to the brain. There it is processed and the appropriate action is decided.

This module provides a basic overview of these mechanisms and the important pain pathways. It will also look at how pain can be modulated at different levels along the pathway.

Note: This is a simplified view of a very complex topic.

## How is pain defined?

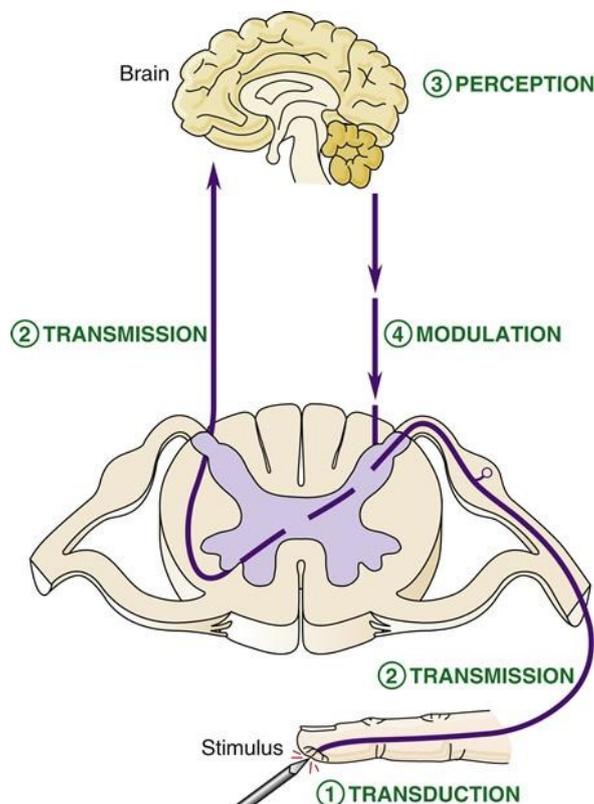
There are many definitions of pain but the two most common ones are, firstly, a definition of pain by Margo McCaffery in 1968 is that *"It's whatever the experiencing person says it is, existing whenever and wherever the person says it does."* Pain is more formally defined by the International Association for the Study of Pain (IASP) as an *"unpleasant sensory or emotional experience associated with the actual or potential tissue damage, or described in terms of such damage"*. Both of these illustrate that pain is more than a physiological process and has emotional and psychological aspects, although it is only the physiological process called nociception, that is covered in this module.

## What is nociception?

A nociceptor or pain receptor is a sensory neuron that responds to damaging or potentially damaging stimuli (transduction) by sending 'possible threat' signals via the spinal cord to the brain (transmission) along the ascending (upwards) pain pathway. If the brain perceives the threat as credible (perception), it creates the sensation of pain to direct attention to the body part, so the threat can hopefully be mitigated or in some cases ignored or reduced (modulation); this whole process is called nociception.

The whole process of nociception can be broken down in to four stages:

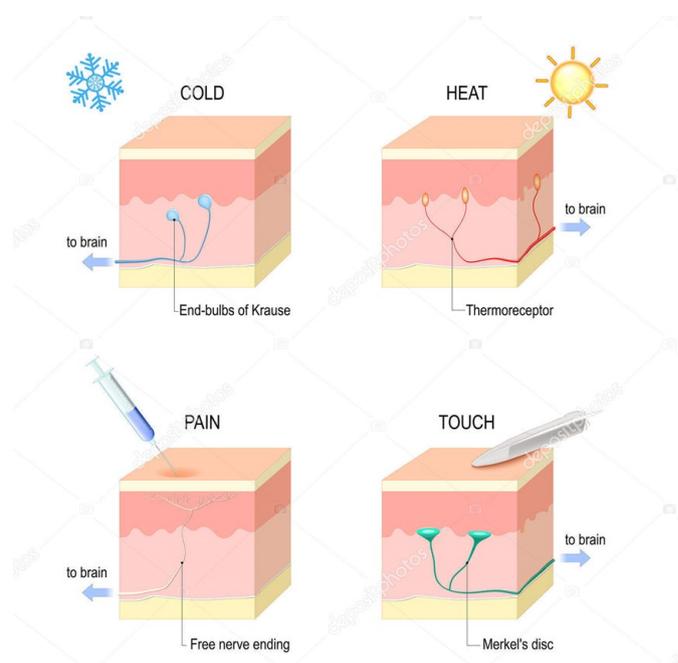
1. Transduction
2. Transmission
3. Perception
4. Modulation



Four processes of pain signalling

## 1. The transduction of pain

As well as normal sensory receptors which respond to touch, pressure, stretch, heat, cold etc., the body contains free nerve ending called **nociceptors** which activate in response to noxious stimuli or pain. Nociceptors convert noxious stimuli into nerve impulses that progress centrally to the spinal cord and then the brain.



Types of sensory neurones

Nociceptors are distributed in the:

- somatic structures (skin, muscles, connective tissue, bones, joints);
- visceral structures (organs such as liver, gastro-intestinal tract but **not** the brain).

Areas such as the fingers have a higher concentration than the forearm, which explains the greater accuracy in determining the location of the pain in sensitive areas.

There are three main types of nociceptors that react to different noxious stimuli:

- Mechanical (pressure, swelling, incision)
- Thermal (burn, scald)
- Chemical (toxic substance, infection, ischemia)

Mechanical and heat stimuli are usually brief, whereas chemical stimuli are normally long lasting.

When cells are damaged, they release numerous chemical mediators and cytokines. If enough are released it results in the activation of the nociceptor and an action potential is initiated causing a nerve impulse. When these impulses are conducted centrally, the second step (transmission) is initiated.

Many of the products produced by tissue damage are also inflammatory and lead to acute inflammation of the damaged area.

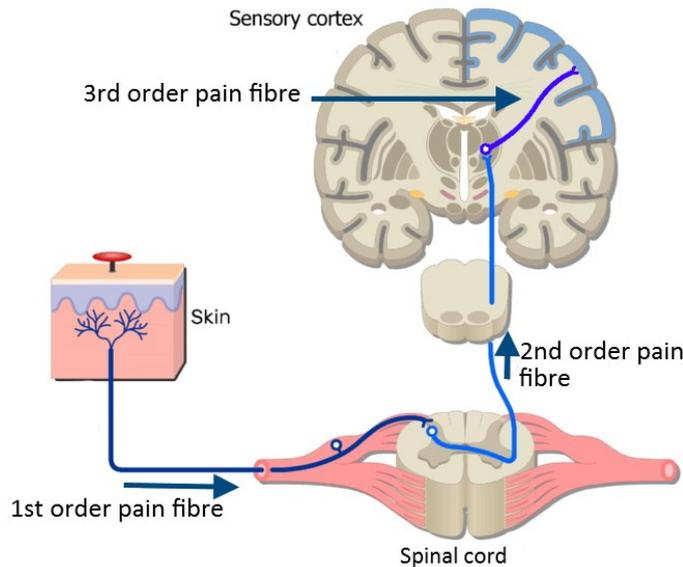
The main chemical mediators released upon tissue damage include:

Prostaglandin	5-HT (Serotonin)
Potassium	Bradykinin
Lactic acid	ATP
Hydrogen ions	Histamine

(This is not a complete list, just some of the more common mediators)

## 2. Transmission

The activation of the nociceptor results in a nerve impulse being transmitted from the site of injury along the pain fibre or neurone to the dorsal (rear) horn of the spinal cord. These are the first order afferent (upwards) pain fibres.



Afferent pain fibres

There are three main types of nerve fibres that send electrical signals to the central nervous system of which two conduct pain. The A-delta and C nerve fibres carry pain and the A-beta fibres carry non-noxious stimuli such as normal touch or vibration. How fast a nerve signal travels up to the brain depends on the characteristics of the fibre. Nerve signals travel faster in larger fibres, and fastest of all when the nerve has a myelin sheath.

- **A-delta (A $\delta$ ) fibres** These myelinated pain fibres have a low threshold for firing and a fast conduction speed. Hence, they are responsible for transmitting the first pain felt. They carry rapid, sharp pain and are responsible for the initial reflex response to acute pain.
- **C fibres** are unmyelinated and small pain fibres therefore conduct more slowly. C fibre activation leads to slow, deep throbbing pain that lingers long after the initial sharp pain abates. The majority of pain sensations travel via C fibres and project to areas of the brain that evoke emotional responses such as displeasure and anxiety. C-fibres have a large receptive area so pain localisation is generally poor.

A-delta fibres	C fibres	A-beta fibres
		
Sharp, fast pain Fast conducting Well localised Thinly myelinated	Dull, aching pain Slow conducting Small Unmyelinated	Light touch Pressure, vibration Highly myelinated
Pain	Pain	Not pain

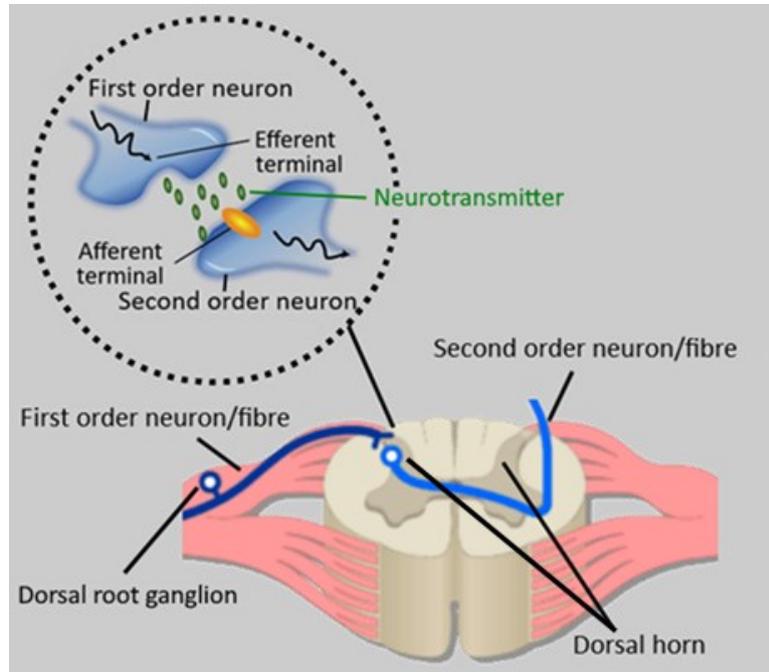
Types of nerve fibres

### Non pain neurones

- **A-beta fibres** are highly myelinated and of large diameter, therefore allowing rapid signal conduction. They are not pain fibres and these mediate the normal sensations of touch, mild pressure, vibration, and joint positioning sensations (proprioception).

### Within the spinal cord

The first order pain fibres enter the dorsal (rear) horn of the spinal cord and cross, where they activate second order afferent pain fibres which then carry the impulse up the contralateral (opposite) side of the spinal cord to the brain. Thus, nociceptor input from the right side of the body travels up the left side of the spinal cord, whereas pain signals from the left side of the body travel on the right side of the spinal cord.



Nerve synapse in the dorsal horn of the spinal cord

Note: The synapses in the spinal cord are extremely complex involving multiple connections with other neurons and interneurons and this is a vastly simplified explanation.

The nerve impulses are transmitted across the synaptic cleft in the spinal cord to the second order pain fibres by neurotransmitters. There are numerous neurotransmitters in the dorsal horn but for our purposes the two important ones are:

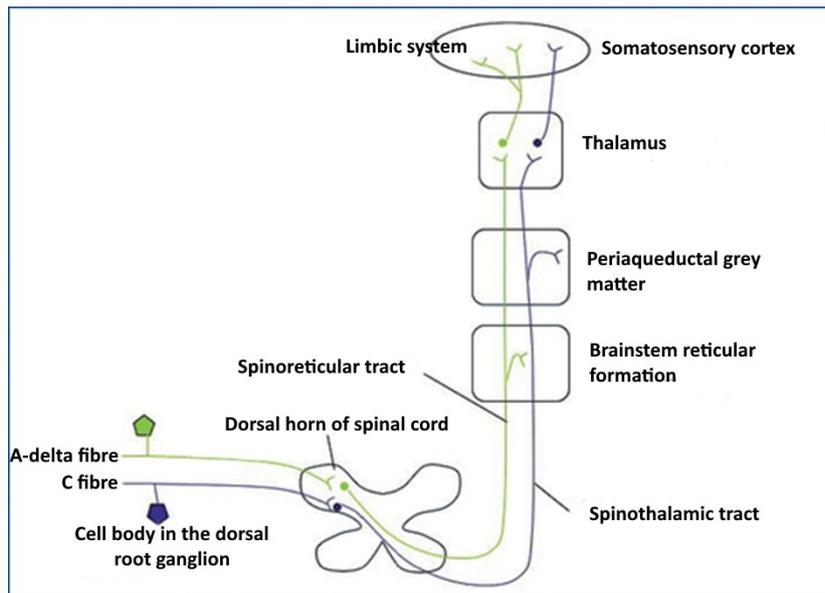
- Substance P the main neurotransmitter for C-fibres.
- Glutamate the main neurotransmitter for A-delta fibres

### Ascending tracts in the spinal cord

The pain impulse is then transmitted up the spinal cord to the brain via two main ascending pathways. These are the **spinothalamic** pathway and the **spinoreticular** pathway.

- **The spinothalamic tract** carries mostly A-delta fibres through the brain stem to the thalamus. Third order pain fibres then ascend to terminate in the somatosensory cortex of the brain. There are also projections to the periaqueductal gray matter (PAG) in the brainstem which has an important role in descending pain moderation.
- **The spinoreticular tract carries mostly** C-fibres, to reach the reticular formation in the brain stem, before continuing to the thalamus and limbic system. This slower pathway plays a role in the memory and emotional components of pain as well as being the origin of the descending pain pathways.

Note: The periaqueductal gray matter (PAG) and reticular formation are explained later in reference to descending pain pathways



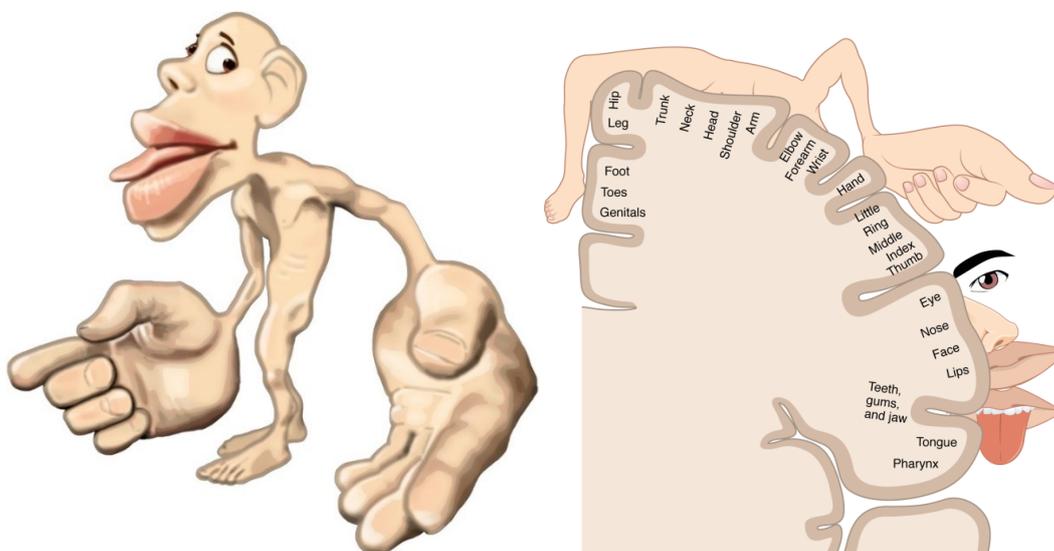
Ascending pain pathways.

### 3. Pain perception or pain processing in the brain

The perception of pain is the end result of pain transmission, when you first become consciously aware of a painful experience. The thalamus, which is the sorting centre for the brain, receives sensory impulses from various parts of the body. These signals are then passed to the relevant somatosensory cortex area of the brain that processes the sensory information and the perception of pain takes place. The somatosensory cortex identifies the nature of the stimulus before it triggers a response, for example, where the pain is, how strong it is and what it feels like, whether we need to 'fight or flight'.

Other areas of the brain such as the limbic system and frontal lobe are also involved and relate the sensation to past experiences, memory and cognitive activities; the emotional experiences of pain.

Because some areas of the body (e.g. lips, hands) are more sensitive to pain than others, they require more circuitry in the cortex to be devoted to processing sensations from them. Thus, the somatotopic maps that explain the somatosensory cortex are distorted such that the highly sensitive areas of the body take up a disproportionate amount of space (see below). This is visually shown as a sensory homunculus.



The sensory homunculus

## 4. Modulation or inhibition of pain transmission

Individuals will respond to identical pain stimulus differently. This is partly explained by modulation or inhibition of an individual's pain. There are many mechanisms that act to inhibit pain transmission within the brain, at spinal cord level and at the peripheral nociceptors.

The evidence for pain modulation was first formally recorded by a physician serving the US Army during World War II, who observed as many as three quarters of badly wounded soldiers reported none to only moderate pain and did not require pain relief medication. According to his report the men were alert and responsive and the injuries were not trivial, including compound fractures and penetrating wounds.

This led him to the conclusion that "strong emotions" block pain. It is now generally accepted that the experience of pain does not solely rely on noxious inputs, but many variables interplay with the experience, including memory, mood, environment, attention and expectation.

Ultimately, this means the resultant pain experienced to the same sensory input can vary considerably. It is the brain's job to weigh all the information and decide whether creating pain is the most appropriate response. This provides a necessary survival function since it allows the pain experience to be altered according to the situation rather than having pain always dominate. For example, if you sprain your ankle running from a lion, the body realises stopping to nurse the injured ankle is not a good survival technique and modifies the pain response to allow you to keep running.

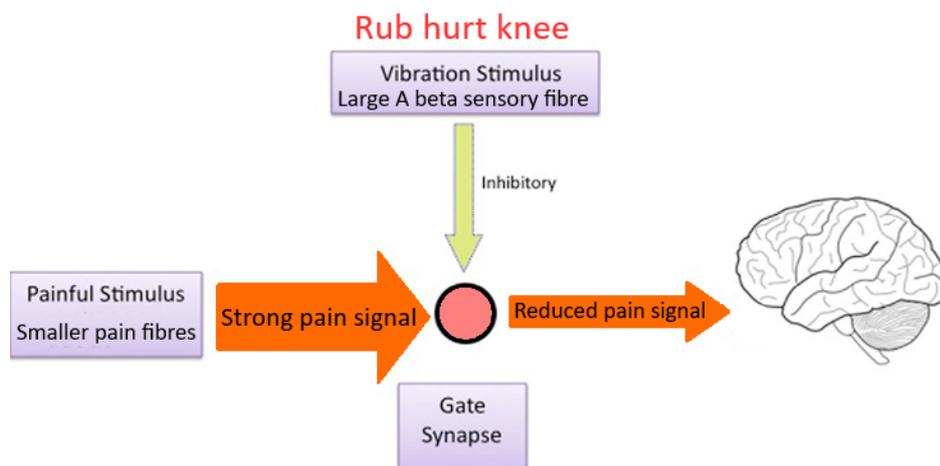
### Gate control theory of pain

The gate control theory of pain was put forward by Ronald Melzack and Patrick Wall in 1965. They proposed that there was a 'gate' mechanism in the central nervous system that opened to allow pain messages through to the brain and closed to prevent them getting through.

When we feel pain, such as when we touch a hot stove, sensory receptors in our skin send a message via nerve fibres (A-delta fibres and C fibres) to the spinal cord and brainstem and then onto the brain where the sensation of pain is registered, the information is processed and the pain is perceived.

The gate theory says that as these pain messages come into the spinal cord and the central nervous system (before they even reach the brain), they can be amplified, turned down or even blocked out. Large diameter sensory nerve fibres (A-beta fibres) responsible for transmitting signals of touch to the brain have the ability to close the pain gate and so block signals from other smaller diameter nerve fibres which transmit pain.

An example of this would be when a child falls over and hurts her knee — if she rubs her knee, the signal from that sensation of touch temporarily blocks the pain signal travelling from the injured knee to the brain.



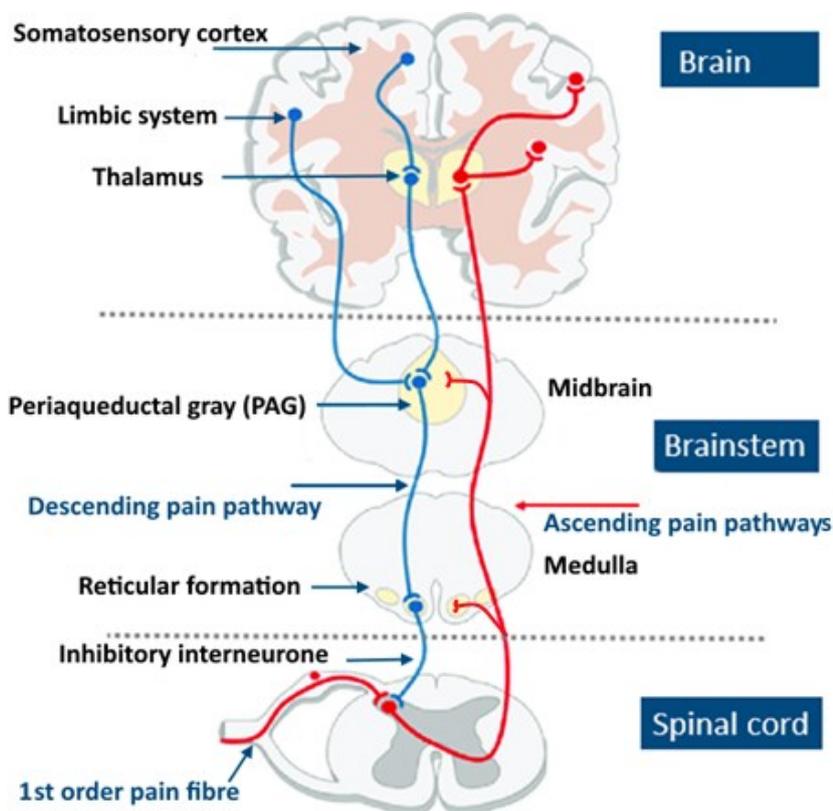
Gate control theory of pain

Despite it having been proved to have flaws in its presentation of neural architecture, the theory of gate control is currently the only theory that accounts for the physical and psychological aspects of pain and so is still used to explain pain modulation.

### Descending analgesic pain pathways

Various areas of the brain feed into the periaqueductal grey matter (PAG), a region of the brainstem that coordinates the body's own analgesic system and is the primary control centre for descending pain modulation. These feeder areas include including ascending pathways, the cerebral cortex, the hypothalamus and the limbic system. They activate the PAG which then signals to the reticular formation to activate the descending inhibitory pathways.

These pathways connect back down to the dorsal horn of the spinal cord where they activate interneurons to inhibit the pain signals arriving at the ascending synapse. They do this by decreasing the production of neurotransmitters glutamate and substance P in the first order pain fibre terminal synapse, reducing the pain signal being sent to the second order neurone. It also inhibits neurotransmitter uptake into the second order pain receptors, thus causing both pre-synaptic and post synaptic inhibition.



Descending pain pathways

### Endogenous opioids

During times of stress, pain, or emotion, the brain creates its own analgesia through the secretion of endogenous opioids from multiple points in the central nervous system. These are classified as endorphins, dynorphins and enkephalins.

Opioid receptors to which these endogenous opioids bind to are distributed throughout the central nervous system. Within the brain, they are found in high concentrations in the cerebral cortex, thalamus, and the midbrain. In the spinal cord, they are found in the dorsal horn where ascending and descend pain fibres pass. Additionally, opioid receptors are found in the gastrointestinal, cardiovascular, endocrine and immune systems.

Endogenous opioids produce analgesia mainly by initiating the various descending pain pathways:

- Opioid receptors block neurotransmitter release (substance P and glutamate) from the nerve fibre terminals in the dorsal horn of the spine.
- They also inhibit post-synaptic neurones from sending signals up the spinal cord to the thalamus.
- Inhibiting peripheral nociceptive nerve fibres, reducing nociceptive transmission from the periphery.
- Activating descending pain pathways in the midbrain.

Overall, this results in reduced neuronal excitability and nociceptive transmission.

### Conclusion

Pain transmission is a result of complex peripheral and central processes but by understanding the four steps of nociception we can begin to understand the complex process of pain transmission. This is essential knowledge for the effective assessment of pain and the selection of appropriate interventions for managing pain.

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