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Review Article

Pain pathway: An overview

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Abstract

Pain is a complex sensory and emotional experience that plays a crucial protective role by signalling potential injury or harm. Derived from the Latin poena (punishment) and Greek poine (price paid, penalty), pain involves both sensory and emotional components, which are influenced by psychological factors such as fear, anxiety, and past experiences. This article presents a comprehensive overview of the anatomical and physiological mechanisms involved in pain perception, emphasizing both ascending and descending pathways of pain modulation.. The ascending pathways, including the spinothalamic tract (STT) and trigeminal pathway, transmit nociceptive signals from peripheral tissues to the brain, where pain is perceived and localized. The descending pathways, originating from brain regions like the "periaqueductal gray" (PAG) and the "nucleus raphe magnus" (NRM), influence pain perception by regulating nociceptive signals at the spinal cord, either enhancing or suppressing their transmission. Key mechanisms such as Diffuse Noxious Inhibitory Control (DNIC), endogenous anti-nociception, and stress-induced analgesia (SIA) contribute to pain modulation. Furthermore, dysfunctions in these pathways can lead to chronic pain conditions, often characterized by central sensitization and failure of inhibitory control. Understanding these pain mechanisms, both in terms of physiology and psychological factors, is essential for developing effective pain management strategies and improving patient care. This review underscores the need for a holistic approach to pain, considering both the neurobiological and psychosocial aspects to enhance therapeutic outcomes.

Keywords: Pain pathways, Nociception, Spinothalamic Tract, Descending inhibition, Chronic pain, Pain modulation, Pain perception.

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1. Introduction

The word pain is traced back to the Old French term "peine", which comes from the Latin "poena", signifying punishment or penalty, and further extending to ideas of torment, struggle, or suffering. Its origin is also linked to the Greek word "poine", denoting a penalty, retribution, or price to be paid.[1,2] Pain serves a crucial biological function by acting as a warning system for potential or actual tissue damage via the nervous system. It encompasses both sensory and emotional dimensions and is influenced by psychological factors such as prior experiences, fear, anxiety, and personal beliefs about pain.[3] Sensory information travels through different pathways in the spinal cord. One pathway, called the dorsal column-medial lemniscus pathway, carries details about fine touch, vibration, proprioception, and pressure via two bundles known as the gracile and cuneate fasciculi.[4,5] (**Figure 1**)

Pain, temperature, and certain touch and pressure signals from sensory nerves terminate in the back part of the spinal cord.[4-6] From there, nerve fibres that are second- or higher-order decussate to the opposite side of the spinal cord and create a pathway known as the "spinothalamic tract".[7] (**Figure 1**) These fibres then travel up to a part of the brain called the ventral posterolateral nucleus of the thalamus, as well as other thalamic areas not depicted here. From the thalamus, these nerve impulses are transmitted to the "somatosensory cortex" in the "postcentral gyrus", the insula, and several additional cortical areas. While traveling through the brainstem, the fibres also give off collateral branches to the "reticular formation".[8]

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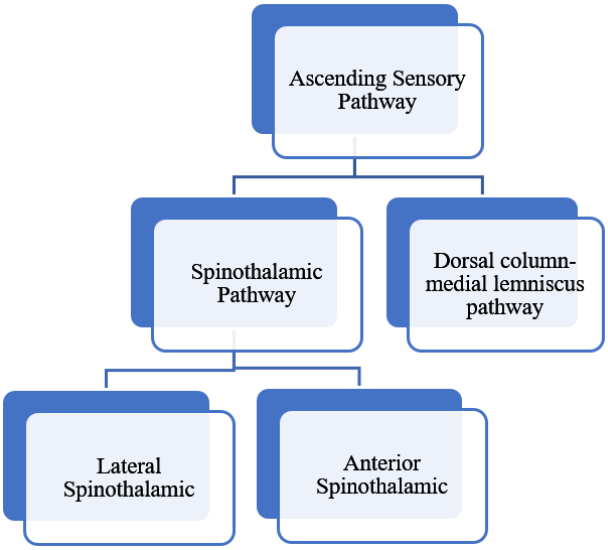

Figure 1:

Lateral spinothalamic tract: Transports sensations of pain, temperature, and basic touch from both somatic and visceral sources.

Anterior spinothalamic tract: Conveys similar sensory information, albeit to a lesser degree than the lateral spinothalamic tract. These pathways play essential roles in transmitting sensory signals from the body to various regions of the brain.

The anterolateral column of the spinal cord is significant in the upward transmission and interpretation of pain signals. Among the ascending pathways, the spinothalamic tract (STT) is considered the primary route for conveying pain sensations in humans.

Nociceptive signals can terminate in the brainstem's reticular formation or in the "periaqueductal gray "(PAG) of the midbrain. Some fibers ascend further to the diencephalon, where they end in the "ventral posterolateral" (VPL) nucleus or the intralaminar nuclei of the thalamus. From there, third-order neurons travel via the posterior limb of the internal capsule and reach the postcentral gyrus and posterior paracentral lobule of the parietal lobe. These somatotopically organized cortical regions are mainly involved in interpreting sharp, well-localized pain.

Before delving into the various types of spinothalamic pathways, it is essential to understand the underlying mechanism of pain perception.

2. Mechanism of Subjective Pain Experience

"Transduction" is the mechanism through which pain stimuli are transformed into electrical signals within the corresponding sensory nerve endings.

"Conduction": in which the nociceptive information is carried by the neuron by way of an action potential to the central terminal of the neuron.

"Transmission": refers to the neural events that carry the nociceptive impulses through synaptic junctions from one neuron to the next.

"Perception": When nociceptive signals arrive at the cortex, they give rise to perception, which in turn triggers a complex network of neuronal interactions within the brain's higher centres.

3. Ascending Pathway of Pain

The pathways that carry information from the spinal cord to the brain are called the ascending pathway. Spinothalamic tract (STT) cells originate primarily in laminae I, III, IV, and V, with some contributions from laminae IX and X (**Figure 2**). Many of these cells cross over across one or two spinal segments, the fibres cross through the central white commissure to the opposite ventrolateral funiculus, from where they ascend as the lateral "spinothalamic tract (STT)". In contrast, deeper dorsal horn neurons give rise to the anterior spinothalamic tract, which also ascends.

A similar pathway exists for nociceptors originating in the face, which arise from the three divisions of the trigeminal nerve. This pathway is known as the "trigeminothalamic tract (TTT)", which starts from nuclei located in the "subnucleus caudalis".

Second-order neurons of the "spinothalamic tract (STT)" and "trigeminothalamic tract (TTT)" arise from the dorsal horn of the spinal cord or brainstem and ascend to synapse in multiple ventral thalamic nuclei. Beyond the STT and TTT, other ascending nociceptive pathways also originate in the dorsal horn, projecting to diverse regions such as the brainstem reticular formation, periaqueductal gray of the midbrain, thalamus, hypothalamus, amygdala, and indirectly to the frontal cortex.[9]

The activation of noxious stimuli in areas distant from the site of tissue damage can trigger the inhibition of the spinothalamic tract (STT) in the dorsal horn. This inhibitory mechanism is known as the diffuse noxious inhibitory control (DNIC) system.[10]

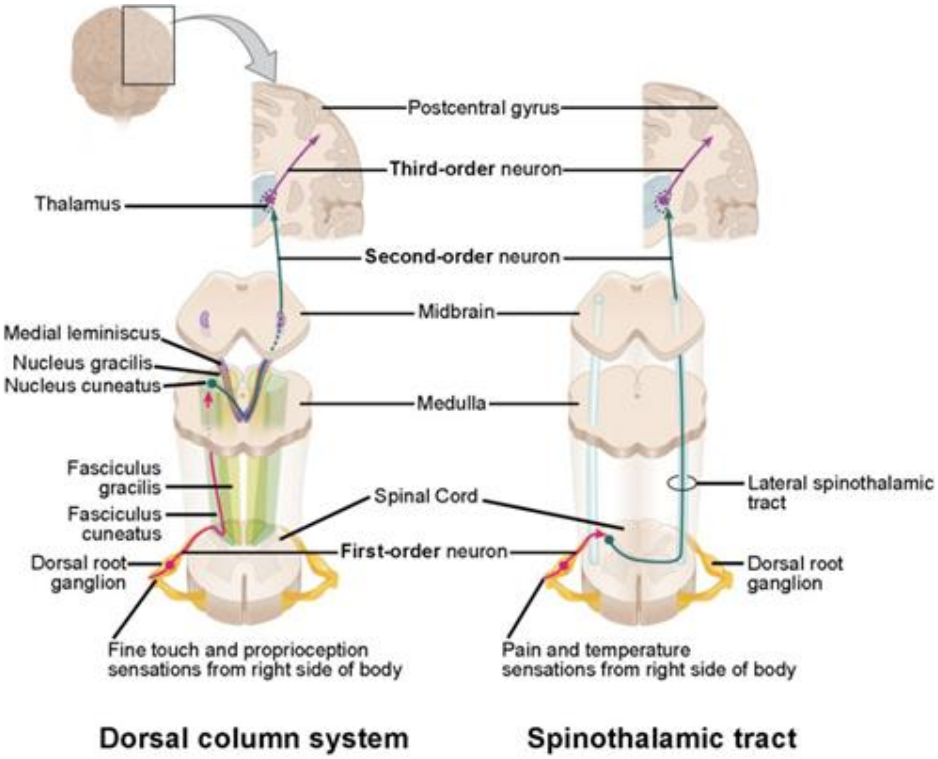

Figure 2: Ascending sensory pathways, OpenStax. Anatomy and Physiology. Houston (TX): OpenStax; [cited 2024 Nov 25]. Available from: https://openstax.org

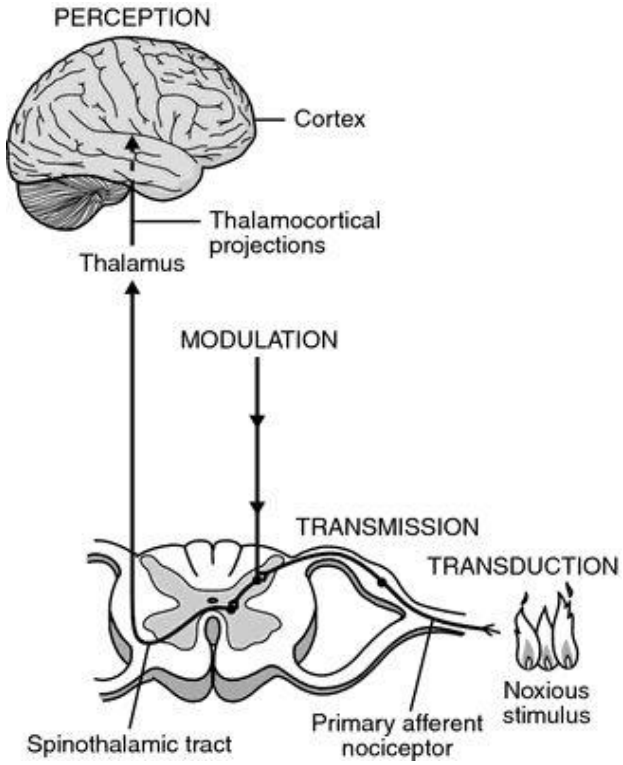

Figure 3: The AmericanHeritage® Medical Dictionary Copyright © 2007, 2004 by Houghton Mifflin Company. Published by Houghton Mifflin Company. All rights reserved.

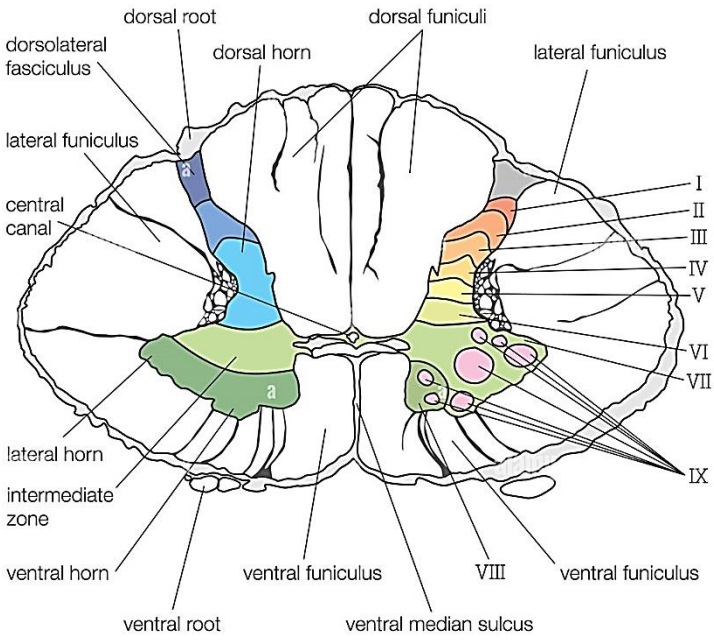

Figure 4: Cross section of spinal cord -Universal Images Group North America LLC/Alamy Stock Photo. Photographer: Encyclopædia Britannica

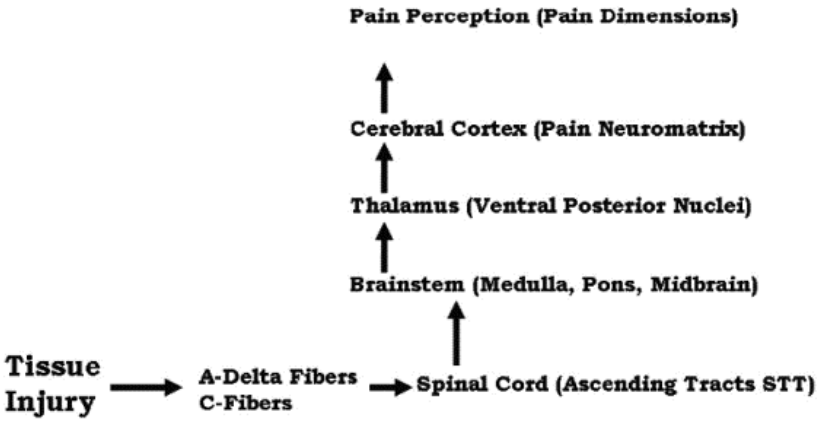

Figure 5: Ascending pain pathway[10]

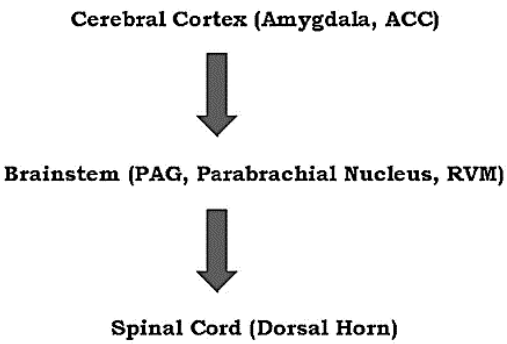

Figure 6: Descending pain pathway[10]

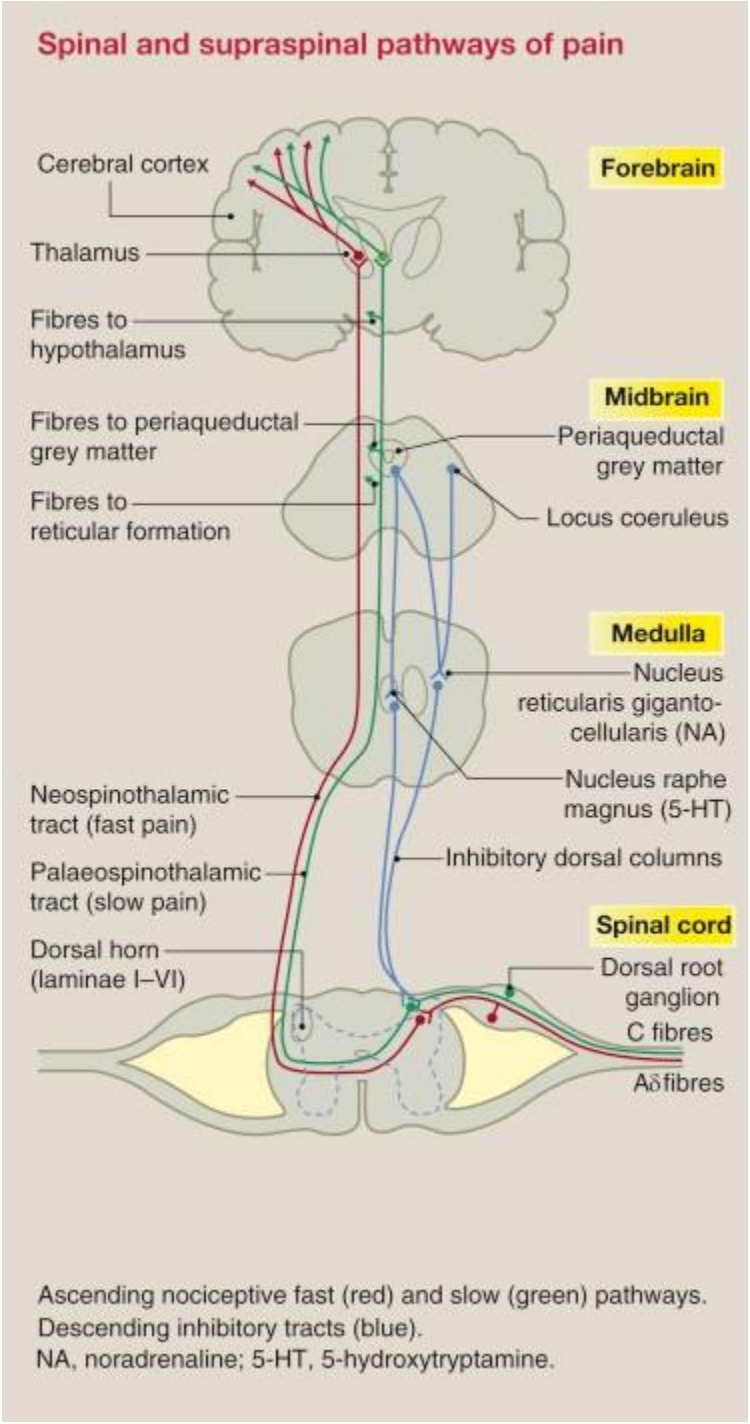

Figure 7: Pain pathway Steeds CE. The anatomy and physiology of pain. Surgery (Oxford). 2009 Dec 1;27(12):507-11

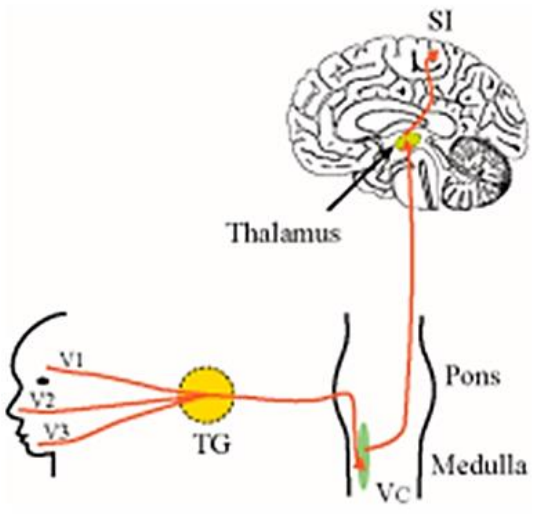

Figure 8: Pain pathway Steeds CE. The anatomy and physiology of pain. Surgery (Oxford). 2009 Dec 1;27(12):507-11

4. Descending Pathway

The descending pain inhibitory system is linked to several neuroanatomical regions, including the cortex, diencephalon, limbic structures, mesencephalic periaqueductal gray (PAG), rostroventral medulla (RVM), nucleus raphe magnus (NRM), and the dorsal horn.[9,10]

Once the ascending nociceptive impulses reach the mesencephalon, they activate the periaqueductal gray (PAG), which plays a key role in modulating pain. The PAG then relays signals to the nucleus raphe magnus, which in turn sends descending fibres to the dorsal horn of the spinal cord. Pain modulation primarily takes place within the dorsal horn of the spinal cord. This descending pathway can exert either inhibitory or facilitatory effects on nociceptive transmission, depending on various physiological and contextual factors.[10,11]

Descending fibres from the nucleus raphe magnus project to laminae I, III, and V of the dorsal horn, where they inhibit nociceptive neurons associated with the spinothalamic, spinoreticular, and spinomesencephalic tracts. Lamina II, also known as the substantia gelatinosa, serves as a critical site for nociceptive modulation. In this region, inhibition is mediated by neurotransmitters such as serotonin (5-HT) and norepinephrine. Additionally, the release of substance P is suppressed either by inhibitory interneurons or through the action of endogenous opioids.[10,11]

Neurons within the nucleus raphe magnus (NRM) and rostroventral medulla (RVM) adjust their firing patterns in response to regulatory signals from higher brain centres. These neurons are functionally categorized based on their activity: "off-cells" are associated with descending pain inhibition (anti-nociceptive), "on-cells" promote pain facilitation (pro-nociceptive), and some neurons remain neutral in their effect.[12,13]

A balance between ascending nociceptive signals and descending inhibitory pathways is essential for an appropriate pain response. Disruption of this equilibrium—such as prolonged nociceptive input, impaired inhibitory control, heightened facilitatory activity, or a combination of these factors—can contribute to the development of chronic pain disorders.[14]

One proposed mechanism underlying the placebo effect involves activation of descending inhibitory pathways that originate from the prefrontal cortex and anterior cingulate cortex. Pain modulation occurs through a complex interplay among various neurotransmitters, their receptors, and neural signals from peripheral inputs, spinal interneurons, and both inhibitory and facilitatory systems within the brainstem. This intrinsic pain-relief network is collectively referred to as the anti-nociceptive system.[15]

Diffuse noxious inhibitory control, which refers to the phenomenon where a noxious stimulus in one part of the body inhibits pain signals in another part. This mechanism involves the activation of inhibitory interneurons in the spinal cord by noxious stimuli, leading to a reduction in pain perception.[16]

The endogenous anti-nociceptive system operates through three key mechanisms:

1. Supraspinal descending inhibition, primarily involving the mesencephalic periaqueductal gray (PAG) and the medullary nucleus raphe magnus, which modulate pain signals at the spinal level.
2. Propriospinal or heterosegmental inhibition, mediated by the mechanism of diffuse noxious inhibitory controls (DNIC), where pain in one area suppresses pain in another.
3. Peripheral mechanisms, including the release of endogenous opioids and the activation of peripheral nerve fibres that contribute to local pain inhibition.[17]

“Stress-induced analgesia (SIA)” has been demonstrated in animals after exposure to stressors such as threat, restraint, rotation, or forced swimming, whereas in humans it can be elicited by experiences like athletic competition, sexual activity, or combat situations. The involvement of endogenous opioids in SIA remains uncertain due to the inconsistent response to naloxone, an opioid antagonist. It's likely that some types of SIA, particularly those induced by continuous sensory input, work to reduce pain transmission.[17]

“Orofacial pain is defined as discomfort within the trigeminal system”. The main distinction between orofacial pain and headaches lies in the specific trigeminal dermatomes affected. Headaches are most often associated with the “ophthalmic branch (V1) “of the trigeminal nerve as well as

the dermatomes supplied by the greater and lesser occipital nerves.[18]

In contrast, according to the "International Classification of Headache Disorders, third edition (ICHD-3)", facial pain is described as pain occurring just below the" infra-orbitomeatal line", in front of the ear, and above the neck. This region is innervated by the "maxillary (V2)" and "mandibular (V3)" branches of the trigeminal nerve. Unlike primary headache disorders, where the headache itself is the primary symptom, facial pain is often secondary in origin, commonly resulting from inflammatory or infectious conditions of the craniofacial region, such as sinusitis or dental pathology. It's worth noting that orofacial pain is present in around 10% of patients with primary headache disorders.[19]

5. Orofacial Pain pathway

The first-order neuron carrying the nociceptive impulses from orofacial structures has stomata in the "trigeminal ganglion". From there, trigeminal fibers enter the pons, descend to the medulla, and synapse in the trigeminal nucleus. After crossing the midline, they ascend as the **"**trigeminothalamic tract (trigeminal lemniscus)".[20]

'A delta fibres' terminate in the parafasiculus (PF) and centromedian (CM) thalamus (PF-CM complex). The PF-CM complex is located within the intralaminar thalamus and is known as the intralaminar nuclei (IL). All of the neospinothalamic fibres terminating in VPL and VPM are somatotropically oriented and from there send axons that synapse on the primary somatosensory cortex (SC I - Brodman area 1&2).

6. Conclusion

Patrick Wall, in 1979, characterized the pain experience as the brain's awareness of a state of need, considering it as one of the qualities among various sensory experiences. He suggested that pain is more of a result or output of brain processing rather than a simple input from the senses.

The pain pathways are controlled by psychophysical, behavioural, and clinical elements. This idea will help us to bring together the clinical data along with the history to manage the pain and improve the quality of life of the patient.

7. Source of Funding

None.

8. Conflict of Interest

None.

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