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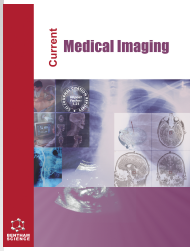

REVIEW ARTICLE

Current Concepts of Pain Pathways: A Brief Review of Anatomy, Physiology, and Medical Imaging

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Abstract:

Background:

Although the essential components of pain pathways have been identified, a thorough comprehension of the interactions necessary for creating focused treatments is still lacking. Such include more standardised methods for measuring pain in clinical and preclinical studies and more representative study populations.

Objective:

This review describes the essential neuroanatomy and neurophysiology of pain nociception and its relation with currently available neuroimaging methods focused on health professionals responsible for treating pain.

Methods:

Conduct a PubMed search of pain pathways using pain-related search terms, selecting the most relevant and updated information.

Results:

Current reviews of pain highlight the importance of their study in different areas from the cellular level, pain types, neuronal plasticity, ascending, descending, and integration pathways to their clinical evaluation and neuroimaging. Advanced neuroimaging techniques such as fMRI, PET, and MEG are used to better understand the neural mechanisms underlying pain processing and identify potential targets for pain therapy.

Conclusion:

The study of pain pathways and neuroimaging methods allows physicians to evaluate and facilitate decision-making related to the pathologies that cause chronic pain. Some identifiable issues include a better understanding of the relationship between pain and mental health, developing more effective interventions for chronic pain's psychological and emotional aspects, and better integrating data from different neuroimaging modalities for the clinical efficacy of new pain therapies.

Keywords: Nociceptive pathways, Pain central nervous system anatomy, Surgical pain approaches, Magnetic resonance imaging, Pain therapies, Neuroimaging modalities.

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1. INTRODUCTION

Pain is defined by the *International Association for the Study of Pain* as "an unpleasant sensory and emotional experience associated with a real or potential tissue injury or described regarding damage" [1]. Pain pathways are complex, dynamic, sensory, cognitive, and behavioural systems that evolved to recognise, integrate, and coordinate a protective reaction to noxious stimuli, involving primitive spinal responses and the complex emotional responses humans consciously experience as pain [1].

Several structures of the Central Nervous System (CNS) compose pain pathways: the spinal cord, thalamus, amygdala, hypothalamus, periaqueductal grey (PAG) matter, basal ganglia, the insular, cingulate cortex, sensory and motor cortices [2]. There is an increasing trend in the publication of articles related to pain pathways [3 - 7], for which an essential knowledge of pain pathways is fundamental.

Pain pathways are significant in clinical applications as they underlie pain perception and provide pain management targets. Understanding the molecular and cellular mechanisms involved in pain processing is essential for developing effective pain therapies. Neuroimaging techniques have also played a critical role in advancing our understanding of pain pathways, particularly in identifying brain regions involved in pain perception and modulation. However, several specific problems are associated with pain pathways and pain management. One significant issue is the lack of effective pain management options for chronic pain, affecting millions worldwide. Many chronic pain conditions do not respond well to traditional pain medications, and there is a need for the development of more effective and targeted therapies [8]. Another issue is the variability in pain perception and responses to pain management interventions. The result of personalised pain management strategies that consider individual differences in pain perception and response is essential [9]. Finally, there is a need for better integration of data from different neuroimaging modalities and more effective data sharing and collaboration across research groups. Developing standardised methods for measuring pain and representative study populations is also crucial. Addressing these problems will help advance our understanding of pain pathways and improve pain management strategies for individuals suffering from acute and chronic pain conditions.

Examining the abovementioned concepts, this review briefly describes the essential imaging neuroanatomy of the pain pathways with relevant clinical implications. This review will be helpful for readers in different medical specialities related to decision-making in pain management. Fig. (**1**) provides a resume of the structures involved in pain pathways.

2. MATERIALS AND METHODS

To conduct a PubMed search of pain pathways, we followed the standard search protocol recommended by the National Library of Medicine. We used the PubMed database, which is free. The search was conducted using the following search terms: "pain pathways," "pain processing," "nociceptive pathways," "neuropathic pain pathways," "chronic pain pathways," "spinal cord pain pathways," "peripheral pain pathways," "spinothalamic tracts" "inflammatory pain pathways," "central pain pathways," "visceral pain pathways," "neuroanatomy," "nociception," "pain management," and "pain theories."

We restricted the search to articles published in English and those available as full-text articles. The inclusion criteria for the studies were: 1) studies that investigated pain pathways in humans or animals, 2) studies that focused on the anatomy, physiology, and function of pain pathways, and 3) studies that investigated the molecular mechanisms involved in pain pathways. The exclusion criteria were: 1) studies that focused on treating pain without investigating the underlying pain pathways and 2) that were not available as full-text articles.

The search results were synthesised and presented in a narrative format, describing the significant pain pathways identified and the key findings from the studies reviewed.

3. ANATOMICAL BASIS OF PAIN

3.1. Peripheral Sensory System

Most sensory receptors respond to only one type of stimulation. Type A, myelinated neurons, and type C, unmyelinated neurons, are the two basic types of nerve fibres. There are two different types of pain transmission: rapid and slow. Aδ-fibres are mainly associated with thermo or mechanoreceptors, which receive and transmit pain quickly. Polymodal receptors have been related to C fibre, and they transmit pain slowly [1].

3.1.1. Sensory Receptors of the Somatosensory System

Cajal [10] describes the somatosensory system and some of the sensory organs that make up the system. Mechanoreceptors are broad and intricately organised, including the Meissner corpuscle, Pacinian corpuscle, Golgi tendon organ, Merkel disk, and Ruffini organs. On the other hand, nociceptors are sensory receptors that respond only to stimuli that cause or threaten to cause damage [11]. Fig. (**2**) shows a diagram of the cutaneous receptors for pain.

3.1.2. Dorsal Roots

The spinal cord receives nerve roots from the peripheral nerves, grouped in the lateral-ventral part of the dorsal root at their entrance to the spinal cord ascent (dorsal root entry zone), the sensory neuron cell bodies are located in the dorsal root ganglia and that is capable of encoding and transmitting information gathered from external stimuli, C fibres may also modulate sensitivity.

3.1.3. Spinal Cord

Most sensory fibres spread from the dorsal root ganglia to the dorsal root entry zone. Most unmyelinated and small myelinated axons project laterally to enter the Lissauer tract (a marginal zone or lawyer of the dorsal horn) and synapse with neurons in the dorsal horn. Aδfibres rise three to four segments in the Lissauer tract before ending in the lamina of Rexed I,

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IIo, or V. In contrast, C fibres normally ascend one segment before terminating in lamina II [1]. Fibres show a somatotopic organisation; being from the dorsal medial, the axons originate in the sacral regions, lower extremities, abdominal, thoracic, brachial, and cervical, and are located in the anterolateral part of the spinal cord [12]. Table **1** summarises the Rexed's laminae, including the name, the Rexed's fibre, localisation, projection, and function.

Lissauer zone also receives collaterals from axons conforming to the posterior columns of the spinal cord that convey proprioceptive information that compete with the entrance of nociceptive information [13].

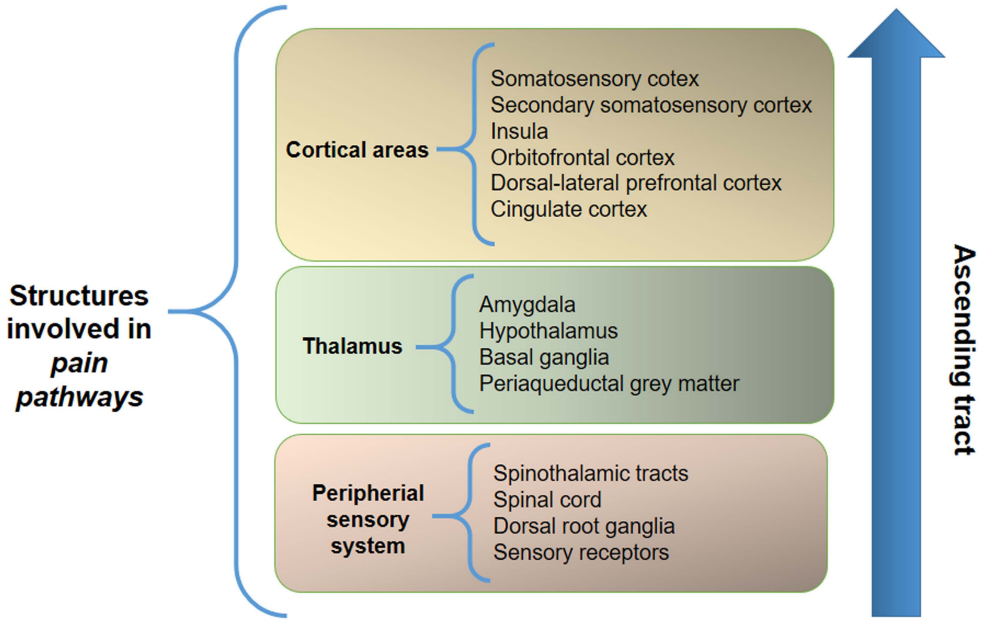

Fig. (1). The structures involved in pain pathways are cortical areas, the thalamus, and the peripheral sensory system.

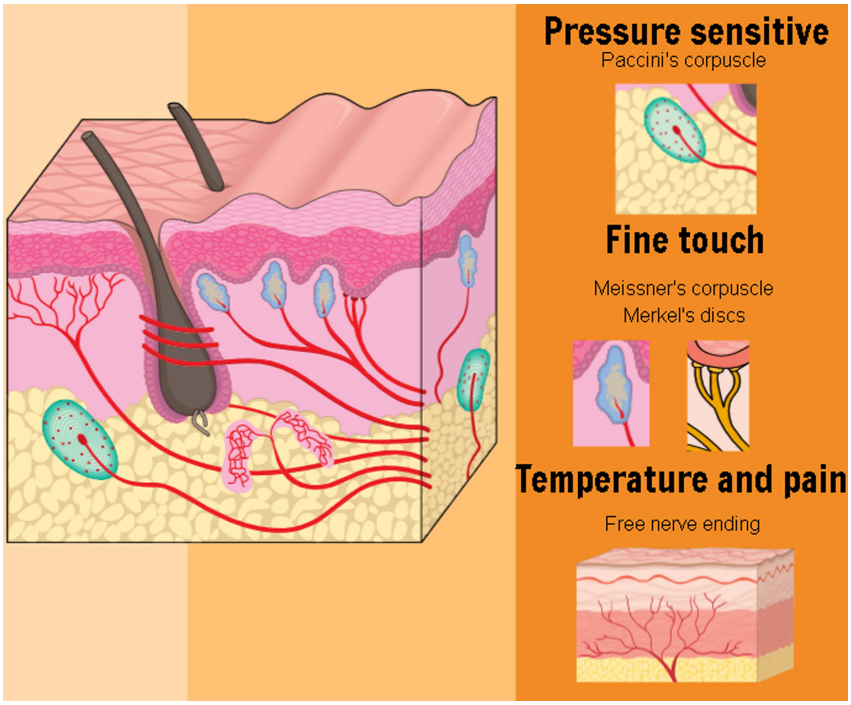

Fig. (2). Cutaneous receptors for pain.

Table 1. Rexed's laminae: type of fibre, local Rexed's projections, and function.

Rexed Lamina	Name	Type of Fibre	Localisation	Projection	Function	References
I	Marginal layer	Aδ	At the tip of the dorsal horn	Its neurons project primarily to the thalamus and brainstem	Nociceptive-specific neurons respond to noxious stimuli, and WDR (wide dynamic range neurons) transmit both noxious and nonnoxious information	[1, 14]
II o (outer)	Substantia gelatinosa	Aδ and C	At the apex of the posterior horn	Lamina II inhibitory neurons project to lamina I, III, and IV.	This lamina is a closed system that influences the projection neurons of other laminae and may play a role in modulating spinothalamic and spinobulbar projections neurons	[1, 14]
II i (inner)		Non-nociceptive				
III	Nucleus propia	Aδ	In the posterior horn	Aδ fibre mechanoreceptive input may have sprouted to lamina I and II	Received proprioceptive and light touch stimuli 1. Pacinian corpuscles 2. Rapidly adaptive mechanoreceptors 3. Type I slowly adaptative mechanoreceptors 4. Type II slowly adaptative mechanoreceptors	[1, 87]
IV		Aα, Aβ, Aδ, and C	Anterior to substancia geltainosa	Its neurons project to the thalamus, lateral cervical nucleus, and dorsal column nuclei. And some neurons project to layer I, which contributes to the integration of sensation		
V		-	The neck of the dorsal horn	The mesial pathways mediating pain's emotional features include WDR neurons with projections to the reticular formation, periaqueductal grey, and medial thalamic nuclei.	These receive proprioceptive information from structures derived from the mesoderm (bones, muscles, joints, ligaments) and data related to the position, movement, and balance of the body	[1]
VI		-	The base of the dorsal horn	Projections from neurons in this lamina probably reach the thalamus or the lateral cervical nucleus.		[1]
VII		-	At the base of the dorsal horn	It contains some well-defined nuclei: lateral intermediate nucleus (T1-L1, medially) and Clarke's dorsal nucleus (T1-L2, laterClarke'som which the posterior spinocerebellar tract and lateral intermediate nucleus arise, in addition to sending information on motor activity to the cerebellum.	Mainly vegetative functions	[1]
IX		Alpha and gamma motor neurons	Size and shape vary between spinal cord levels	Alpha motor neurons innervate the extrafusal muscle fibres responsible for the motor act, and gamma motor neurons innervate the intrafusal muscle fibres maintaining tone and posture.		[1, 88]
VIII		Motor interneurons	Commissural nucleus	-	Detects painful muscular stimuli and innocuous mechanical stimuli.	[1]
X		-	Surrounds the central spinal canal	Axons decussate from another side of the spinal cord to the other	Receive direct input from Aδ fibres and could play a role in nociception integration.	[1]

Table 2. Nervous tracts are involved in pain pathways.

Anterolateral Pathway of Pain			
Division	**Termination**	**Function**	**Example**
Spinothalamic tract	Mainly to the ventral posterior lateral nucleus (VPL) Others: intralaminar thalamic nuclei and medial thalamic nuclei.	Mediates the sensitivity of pain and temperature sensation, such as the location and intensity of the stimulus.	If you hit your right foot on a rock, your spinothalamic tract can tell you that "something hard and solid hit the sole "of your right foot."
Spinoreticular tract	The medullary-pontine reticular formation projects to the intralaminar thalamic nuclei.	Carries the emotional features of pain.	Your spinothalamic intralaminar projections and the spinoreticular tract make you feel, "Ouch, that hurts".

(Table 2) contd.....

Anterolateral Pathway of Pain			
Division	**Termination**	**Function**	**Example**
Spinomesencephalic tract	Periaqueductal grey matter and the superior colliculus.	Participates in central modulation of pain.	Your spinomesencephalic tract takes over pain modulation, allowing you eventually to think, "Ah! That feels better".

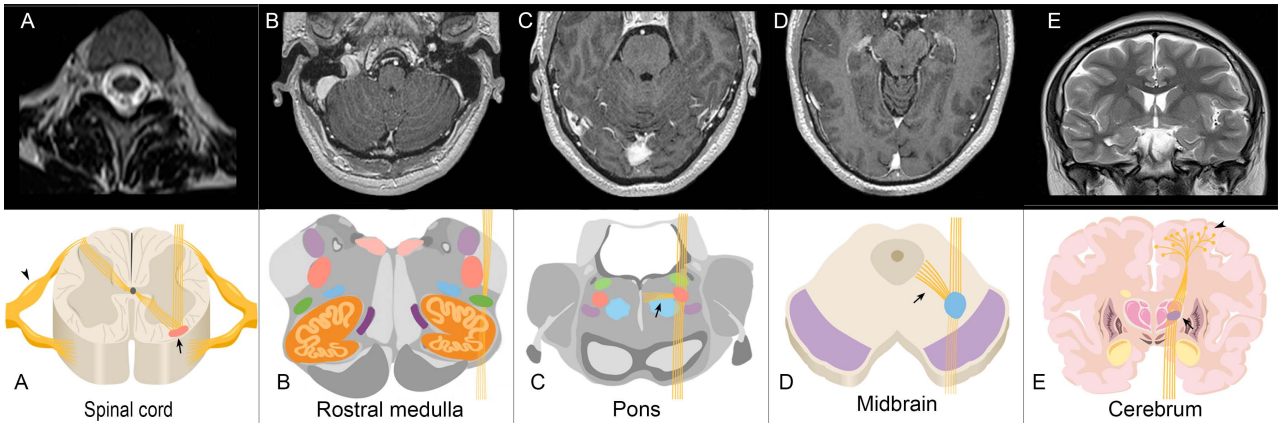

Fig. (3). Schematic diagram and MRI visualisation of the anterolateral tract. (**A**), represent the spinal cord, anterolateral pathway (black arrow), and dorsal root ganglia (black arrowhead). (**B**), represent the rostral medulla. (**C**), represents the pons and the spinoreticular tract (black arrow). (**D**), represents the midbrain and spinomesencephalic tract (black arrow). (**E**). represent the cerebrum and ventroposterior lateral nucleus of the thalamus (black arrow) and somatosensory cortex (black arrowhead).

3.2. Spinothalamic Tracts

The spinal dorsal horn's neurons process sensory information, which is then sent across many brain regions, including pain perception. Primary afferents that innervate the skin and more profound issues of the body send sensory information to the dorsal horn neurons, which respond to certain stimuli. Their sensory modality determines the distribution pattern of these afferents in the dorsal horn and the body location they innervate [1, 14]. Table **2** shows the nervous tracts involved in pain pathways.

The axonal terminals of the first neuron follow a characteristic pattern depending on the receptor type. Large-caliber myelinated afferent fibres (Aβ) that are connected to low-threshold cutaneous mechanoreceptors end in laminae III, IV, and V (called "nucleus propius") and in the dorsal "portion of lamina" VI. The Aβ fibres end mainly in the laminae I (marginal zone) and V. In contrast, the C-type fibres terminate almost exclusively in the ipsilateral lamina II. However, a few have terminations in the ventral region of lamina I and the dorsal area from lamina III. The fibres of the muscular and joint nociceptors end in laminae I, V, and VI. In contrast, the visceral nociceptor C fibres do so in laminae I, V, and X, and some in the contralateral lamina V. Therefore, lamina II (Rolando gelatinous substance) receives only cutaneous nociceptor terminations of C fibres [15].

The spinothalamic pathways are oriented vertically along the ventrolateral portion of the spinal cord and are the main conduit of the peripheral nerves. They receive projections from the contralateral lamina I, IV, and VI. It consists of two sections: the dorsolateral, which carries axons from the superficial, and the ventrolateral lamina of the deep lamina [16]. The fibres project to the posterolateral ventral nuclei (VPL of the thalamus) that originate in laminae I and V neurons and participate in the discriminative sensory aspects of pain signalling. Deep dorsal nuclei at the medial level of the thalamus retransmit the motivational and affective components of the noxious stimuli (of the cingulate gyrus) [17]. The lamina V, VII, and VIII neurons have direct projections to the nuclei of the reticular substance [18]. The electrical activation of the gelatinous substance of Rolando is based on the activation of afferent fibres responsible for inhibiting the transmission of nociceptive information at the segmental level in the place of application of the electrical stimulus, which serves as the basis in the neuromodulation techniques.

These crossed second-order axons ascend in the spinal cord and brainstem as the spinothalamic tract. The more significant part of the spinothalamic tract ends in the reticular formation. However, another part continues without a relay to the thalamus [17]. Fig. (**3**) shows the anterolateral pathway (spinothalamic pathway system) that represents the system from the cutaneous receptor to the postcentral gyrus (somatosensory cortex).

3.3. Brain Tracts Participating in the Pain

After activation of the nociceptors, noxious input ascends via the spinothalamic path to the thalamus, specifically the VPL nucleus. Although this has not been confirmed, and the spinothalamic tract seems to end behind the medial lemniscus in a nucleus basal and posterior to VPL, labelled in the stereotactic atlas of the human brain Ventralis Caudalis Parvocellularis (Vcpc) [19], that also receives collaterals from axons of the medial lemniscus ending in VPL that convey proprioceptive information. At this level, sensory information is relayed from the thalamus to the amygdala, hypothalamus,

periaqueductal grey matter, basal ganglia, and cortex, specifically to the insula, the cingulate, and the parietal cortex generating the subjective experience and, as a whole, the perception of pain [20].

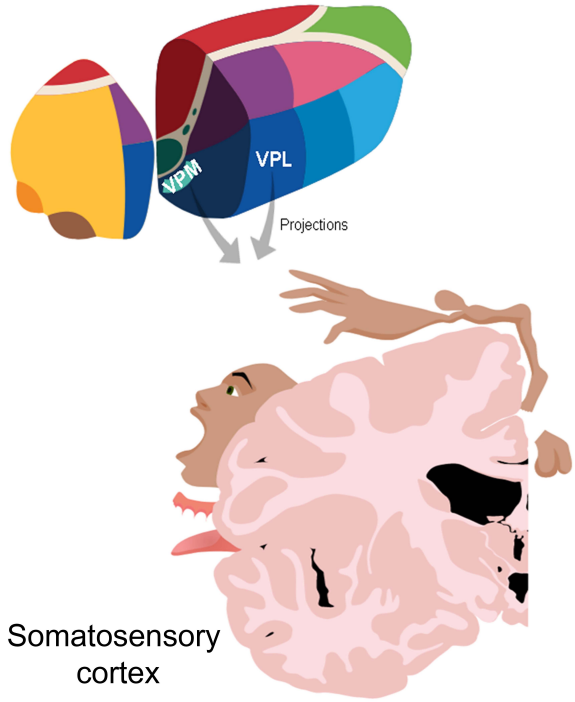

Fig. (4). Thalamus' primary nuclei are involved in pain. The ascending tract arrives at the VP, composed of nociceptive-specific neurons with contralateral receptive fields and receives projection from lamina I neurons, and is connected to the insula and region 3a in the brain.

3.3.1. Thalamus

The sensory thalamus is divided into nuclei that roughly maintain the periphery's segmentation into noxious periphery divisions.

Ventroposterior (VP) thalamic nuclei are the most direct subcortical relay site for the spinothalamic and trigeminal thalamic tract before relaying pain signals to the primary sensory cortex. This nucleus is somatotopically arranged, with neurons stimulated medially by face stimulation (ventroposterior medial, VPM) and laterally by arm and leg stimulation (ventroposterior lateral, VPL). The VP is divided into a core that responds to mechanical, non-toxic stimuli and an inferior posterior area that transmits nociceptive signals. The VPM nucleus is crucial in pain processing; it comprises nociceptive-specific neurons with contralateral receptive fields and receives projection from lamina I neurons. The VPM neurons are connected to the insula and region 3a in the brain [1]. Pain is also transmitted through the thalamus' central nuclei. The intralaminar thalamus' is where neurons from the spinothalamic tract terminate. Indirect projections from the parabrachial nucleus and brainstem reticular nuclei are also received by the intralaminar thalamic nuclei, which are critical in pain processing [1]. Fig. (**4**) shows the primary thalamus nuclei involved in pain.

3.3.2. Cortical Areas Involved in Pain Pathways

With the introduction of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), it has become clear that other telencephalic regions are activated during acute noxious stimulation, such as the motor and premotor cortices, the cerebellar cortex, and the striatum.

The primary and secondary somatosensory cortices constitute the lateral system. These areas are responsible for comprehending the location and strength of a nociceptive stimulus. The insula and anterior cingulate cortex generate the medial approach. The anterior cingulate cortex is implicated in the affective aspect of pain perception and cognitive and evaluative functions. The insula appears more complicated because it participates in the affective component and processes information on nociception intensity and localisation. It is also a communication centre between the lateral and medial systems [21].

3.3.3. Brain Gyri Participating in Pain Perception

Painful stimuli activate distant cortical regions, including the primary somatosensory cortex (Brodmann areas 3a, 3b, 2, 1, postcentral gyrus), secondary somatosensory cortex, insula, orbitofrontal cortex, dorsal-lateral prefrontal cortex, extended amygdala, and cingulate cortex [1].

The somatosensory cortex (SI) is involved in the discriminative quality of pain, and the secondary somatosensory cortex (SII) receives projections from the ventrobasal thalamus, the VPM-VPL, and the somatosensory cortex. The responses of neurons between SII and Broadmann's area 7 are related to the noxious stimuli [1].

The insula receives input from the SI, SII, VPI, pulvinar, central median, and parafascicular nuclei; VPM can provide a graded response proportionate to the noxious stimuli' severity implicated in sensory-discriminative pain processing [1].

The midline and intralaminar thalamic nuclei (MITN) project to the limbic cortex, the periaqueductal grey matter, the amygdala, and the anterior cingulate cortex (ACC). Also, the anterior insula may be between the two pain systems and participates in processing aspects associated with each, including sensory coding, body condition assessment, and autonomic regulation. It also highlights that various thalamic nuclei project along the cingulate cortex instead of a single nociceptive nucleus. The ACC and middle cingulate cortex receive projections from the medial and intralaminar thalamic nuclei. As a result, the final pain experience is influenced by sensory stimuli and cognitive and behavioural perceptions of pain, which involve several previous experiences, injuries, and cultural backgrounds [1].

3.4. Descending Pathways

Incoming signals from noxious stimuli are primarily regulated by descending pathways in the brain through synapses on dorsal horn (DH) neurons. These pathways include the rostral ventromedial medulla (RVM), the dorsolateral pontomesencephalic tegmentum, and the PAG region. The thalamus' central nuclei are the outer projections (centrolateral, paraventricular, parafascicular, and central medial areas,

including the tegmental area and substantia nigra pars compacta) [1]. The PAG-RVM's route is a descending pain modulatory system that generates analgesia. It suppresses the painful signal response of lamina V interneurons, and the PAG is implicated in ascending regulation of nociception and behavioural response integration [1].

4. PHYSIOLOGY OF PAIN

Nociception is an information process ranging from the noxious stimulus's reception to its passage through the peripheral nerves to the central nervous system. Nociception is possible thanks to the receptors ending in the dorsal horn of the spinal cord and sensitive to various mechanical and thermal stimulation signals modulated by inflammatory and biochemical agents [22]. Table **3** depicts the mediators associated with pain perception.

4.1. Cellular Anatomy

Conveying pain sensations range from 0.5 to 20 microns in diameter and can drive impulses between 0.5 to 120m / sec. At larger neuronal diameter, higher conduction velocity. Type A neurons detect and transmit pain rapidly and lead to rates of 6 to 30 m/second, and are associated with thermoreceptors and mechanoreceptors. In contrast, type C fibres do so at rates of 0.5 to 2m/second and are related to polymodal receptors, so their participation in tissues [1].

There are four steps in the process. The first is a transition, which happens when painful stimuli activate primary afferent neurons in peripheral axons. Vanilloid receptor 1, which response to temperature, capsaicin, and protons, and Mas-related G protein-coupled receptors, which mediate nociceptive behaviour to mechanical stimuli, are located on these axons [22].

Transmission, which involves Aδ and C fibres, is the next step in the pain pathway. Aδ fibres synapse with neurons in laminas I and V, while C fibres synapse with neurons in laminas I and II in the dorsal horn of the spinal cord [22]. Fig. (**5**) represents the fibres (Aβ, Aδ, and C) involved in pain transmission.

Table 3. Mediators associated with pain perception [89, 90].

Mediators related to Pain Perception	
Inflammatory and Vasoactive Mediators	Inflammatory and vasoactive mediators such as histamine, substance P, prostaglandins, bradykinin, serotonin, and nitric oxide are released into the bloodstream
Receptors	Toll-like receptors, PAR receptors, glutamate receptors, AMPA receptors, NMDA receptors, and, most of all, opioid receptors TRPV1
Ion channels	Channels include voltage-gated sodium channels (NaV channels), voltage-gated calcium channels (VGCC), potassium channels, and TRP channels

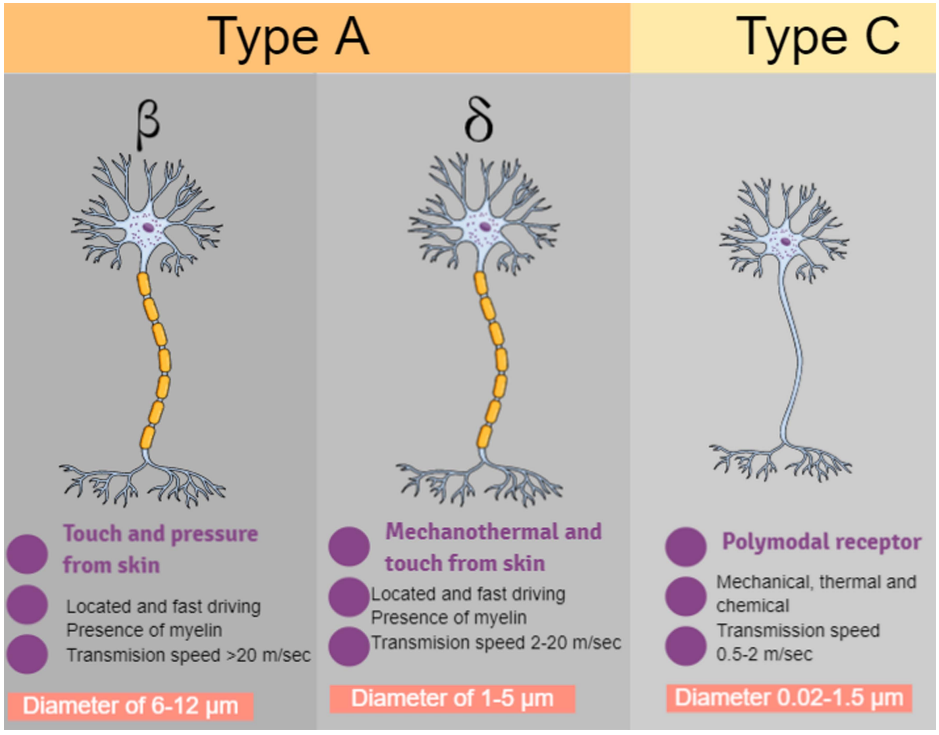

Fig. (5). Types of nerve fibres related to pain transmission [1, 20].

Second-order neurons transmit information to the central nervous system via the lateral and medial spinothalamic tracts. The ventral posterolateral nucleus of the thalamus receives information from the lateral spinothalamic tract, which notifies the brain about the location and severity of the pain; the autonomic and unpleasant emotional perception of pain is transmitted via the medial spinothalamic tract, which projects to the medial thalamus [22].

Third-order neurons in the thalamus then project to particular cortical areas that control pain perception, localisation, and feelings [22].

4.2. Neurochemistry of Pain

When activated by a nociceptive stimulus, the nociceptors transmit the information through the neurotransmitter glutamate; also, at the site of injury, near the receptor, there is a high amount of sodium receptors whose expression can alter the sensitivity of the nerve endings of fibres. Also, they play a role in central sensitivity and can contribute to hypersensitivity [23].

Inflammatory mediators such as bradykinin, serotonin, interleukins, and prostaglandins are secreted, resulting in decreased excitation of the activation threshold, thus initiating a neurogenic inflammation process [24]. Fig. (**6**) shows a schematic diagram of inflammatory mediators involved in pain transmission as the initial steps triggered by pain stimuli.

It is a process by which active nociceptors release neurotransmitters to induce vasodilation and thereby stimulate the immune system cells to perpetuate the cycle [12]. However, the complex interactions between the brainstem pathways and their receptors modulate pain inhibition and facilitation. These pathways also modulate the noradrenergic neurons, their terminals in the dorsal reticular nucleus of the brain stem or the thalamus, medial prefrontal cortex, dorsal horn spinal cord, and trigeminal spinal caudalis. They participate in developing and maintaining *allodynia*, which is the perception of any sensory information as painful, hyperalgesia after a nerve injury [25], the release of norepinephrine, and projects to the thalamus. Norepinephrine regulates the addition of nociceptive input by modulating transmission to other cortical and subcortical regions [26].

Now, every stimulus has a counterpart; in this case, the descending pain modulatory system governs the endogenous secretion of opioids [16, 27]. The system of endogenous pain modulation is composed of intermediate neurons within the superficial layer of the dorsal horn of the spinal cord and descending neural tracts, which can inhibit the pain signal. Exogenous and endogenous opioids can act on the presynaptic terminals of the primary afferent nociceptors via the opioid receptor through an indirect blockade of the calcium channels and the opening of the potassium channels [28]. The inhibition of the calcium entry in the presynaptic terminals and the exit of potassium results in hyperpolarisation with inhibition of pain neurotransmitter release in analgesia. Activation of the cortical descending neural system involves the release of neurotransmitters: β-endorphins, enkephalins, and dynorphins. These peptides relieve pain even in stressful situations [29, 30]. A simplified global schematic diagram of the pain pathway is presented in Fig. (**7**).

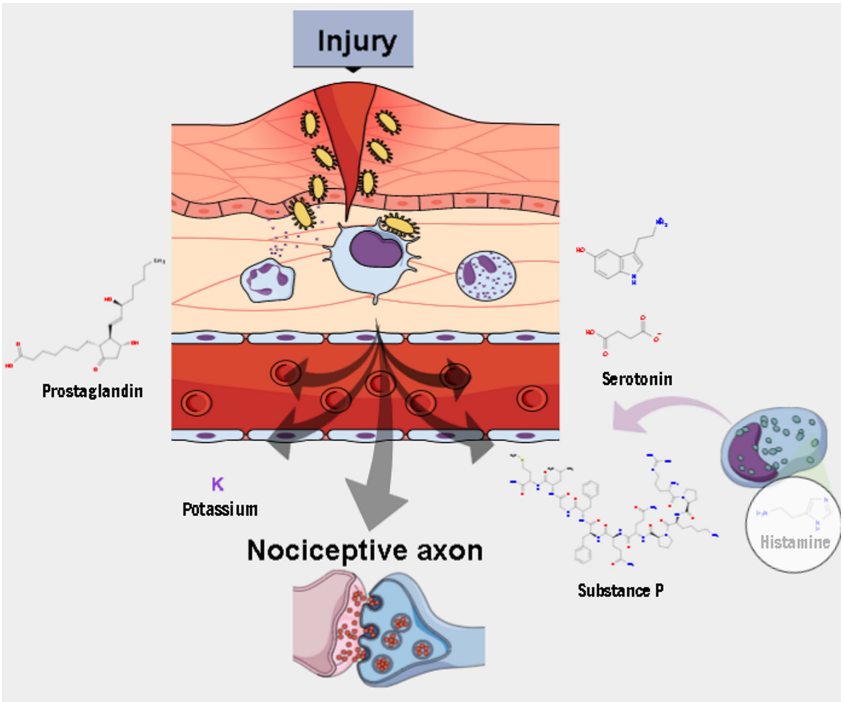

Fig. (6). Inflammatory mediators associated with pain transmission.

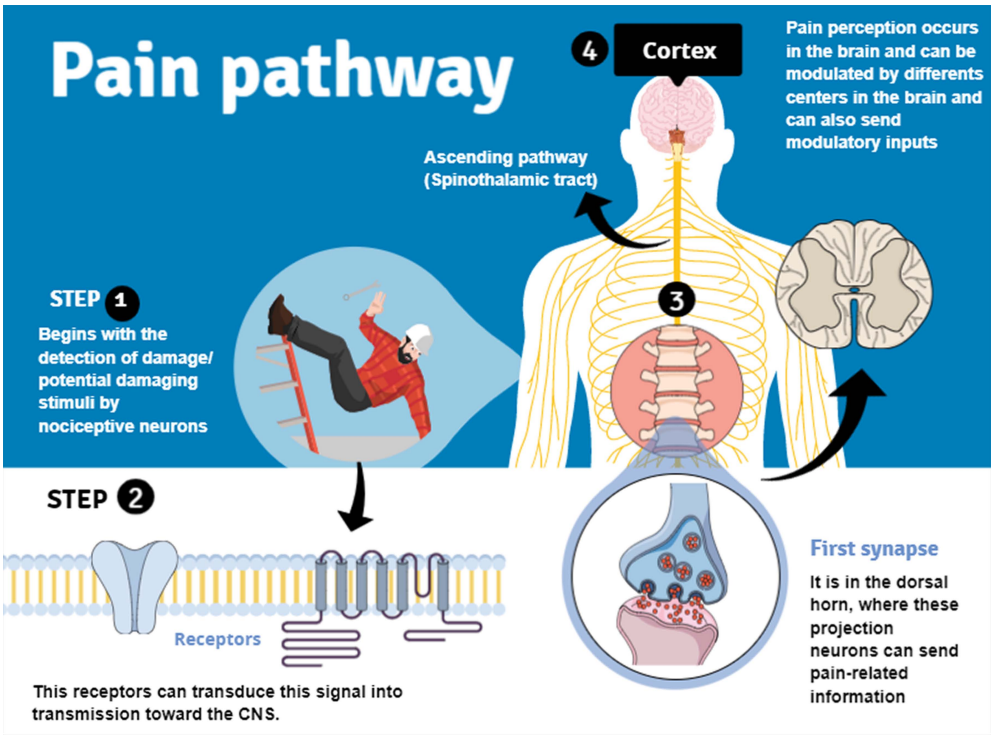

Fig. (7). Simplified schematic diagram of the pain pathway.

Table 4. Functions and limitations of the primary imaging modalities currently used to study pain pathways.

Modality	Function	Limitations	References
Position Electron Tomography (PET)	Since the mid-1970s, PET techniques have been used to map the brain circuits that control pain perception. bold fMRI has practically substituted this approach.	• Temporal resolution is limited. • Unwillingness to measure brief periods. • Accessibility is necessary. • Intravenous injection is needed.	[21]
Functional Magnetic Resonance Imaging (fMRI)- Blood oxygenation Level Dependent (bold)	fMRI is focused on using signal changes associated with variations in blood oxygen levels, an indirect measure of activation-induced changes in cerebral perfusion. Because of many drawbacks, fMRI is not a good approach for monitoring painful stimuli over lengthy periods.	• Only effects on brain activity are detected. • "MRI-compatible" patients and equipment are requested. • Due to low-frequency magnetic fluctuation, sensitivity decreases when sampling time passes 1 minute after baseline.	[21]
Functional Magnetic Resonance Imaging (fMRI)- Arterial Spin Labeling (ASL)	This technique, which has been used since the 1990s, may directly quantify blood flow within the cortex by obtaining two successive pictures, one with the arterial blood H2O polarity inverted and the other without.	• Compared to fMRI-bold, the imaging volumes are smaller, and the sensitivity is lower.	[21]
Magnetic Resonance Spectroscopy	Studies of biomarkers confirmed that grey matter decreases not due to compromised neuronal viability.	-	[33,34]
Tractography	The procedure is used to reveal the neural tracts. It uses special magnetic resonance imaging techniques and has the potential to play a complementary role in the clinical evaluation of pain, being able to determine the neurological level of deterioration and predict long-term neurological results associated with pain.	• This MRI sequence shows the structural scaffold of brain fibres.	[33,34]

5. IMAGING MODALITIES

It has been 50 years since the first imaging method was proposed to study pain pathways [20]. The study of the functional anatomy of pain was initially founded on positron emission tomography (PET) [1, 3 - 5]. In recent years more interest has been focused on the use of functional magnetic resonance imaging (fMRI), particularly blood oxygenation level-dependent (BOLD) and arterial spin labelling (ASL), as modalities for the mapping of the cortical response to various pain states [2, 6, 7, 31, 32]. Table **4** summarises the main functions and limitations of the current imaging methods used to study pain pathways.

5.1. The Relevance of MRI Techniques in the Evaluation of Pain

There is evidence of the relationship between chronic pain and the decrease in the volume of grey matter in various structures, such as the thalamus and insular cortex, but more consistently, the medial prefrontal cortex [33, 34] demonstrated using fMRI [35]. The latter structure is also affected by psycho-affective comorbidities such as depression and anxiety. Fig. (**8**) shows the most common gyri assessed in recent pain literature.

Several morphometric studies based on longitudinal voxels have demonstrated the reversibility of grey matter volume after successful treatment and elimination of chronic pain in the amygdala, thalamus, brainstem, anterior cingulate cortex, dorsolateral medial prefrontal cortex, and insular cortex [34, 36], as is the case with Primary Sensory Areas such as Area 3a is found in the depth of the central sulcus. It follows this sulcus up to the midline but does not fold onto the medial face of the hemisphere; it is known to receive sensory information from deep body tissues [37]. This area also involves the deep somatic tissue's burning and chronic pain sensations. Chronic pain sensations suggest that area 3a has relevance in many chronic pain ailments observed in the clinical setting [38]. The study and identification of pain pathways using imaging techniques such as MRI and tractography allow us to identify and facilitate decisions about treating chronic pain. The knowledge of neuroanatomy is growing, partly due to the contributions of neuroimaging studies. To deepen these and their clinical application is an important task, so with this brief review, we offer an alternative for treating pain neuroanatomy in the clinic. Fig. (**9**) shows an MRI tractography of the spinothalamic tract.

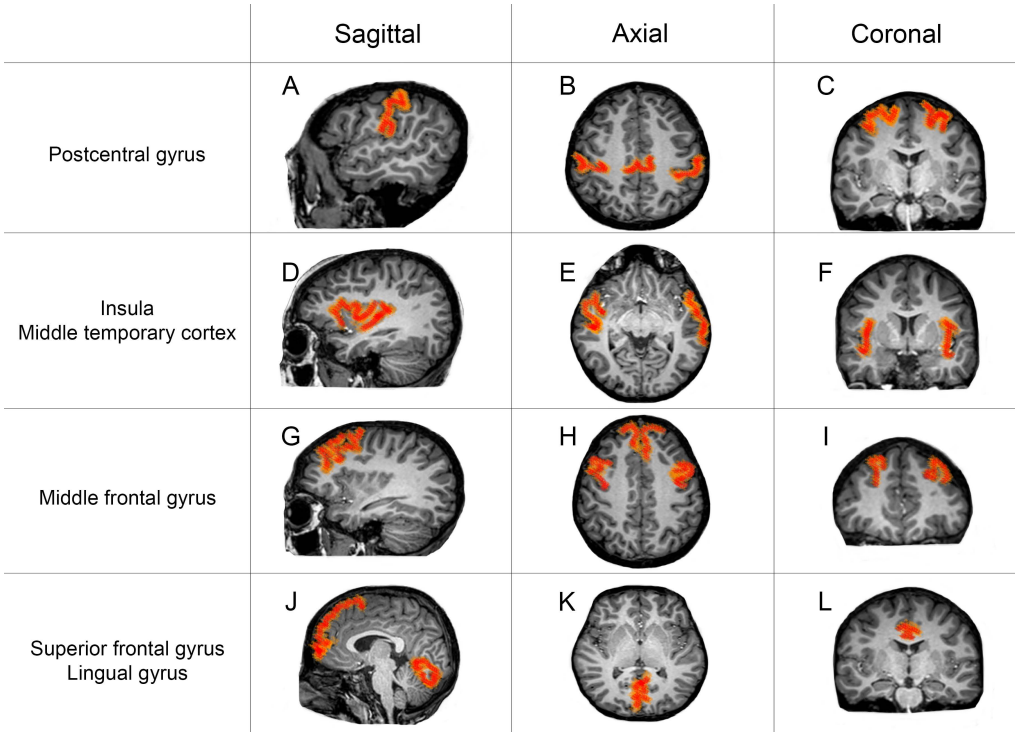

Fig. (8). (**A**, **B**, **C**): Postcentral gyrus. (**D**, **F**): insula. (**E**): Middle temporary cortex. (**G**, **H**, **I**): middle frontal gyrus. (**J**): Superior frontal gyrus and lingual gyrus. (**K**, **L**): Lingual gyrus.

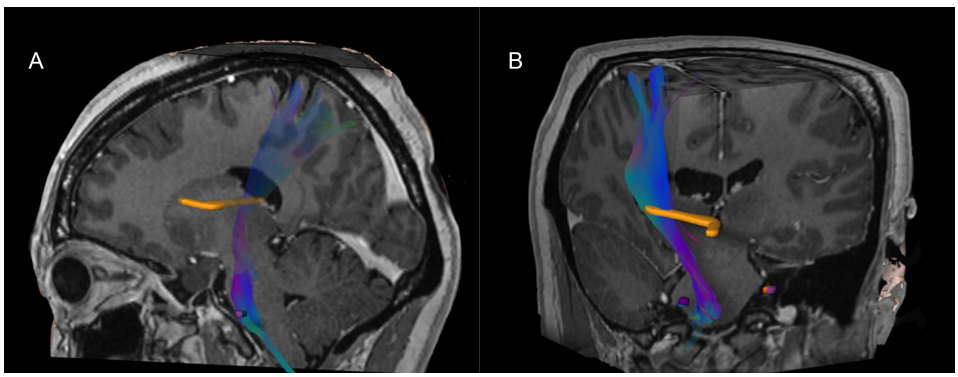

Fig. (9). MRI tractography of the spinothalamic tract (blue tracts). (**A**), Sagittal view. (**B**), Coronal and oblique view. A partial view of the internal capsule is visualised in yellow colour.

Table 5. Main theories about pain perception [42, 43].

Theory	Postulate
Specificity of pain	Both touch and pain are encoded in separate ways so that specialised sensory organs encode their stimuli. The impulses for each modality are transmitted by different routes and are projected toward the brain's centres of contact and pain, respectively.
Pain intensity	There are no different pathways for high and low threshold stimuli. Still, the number of neuronal impulses determines its magnitude of it. First-order afferent neurons synapse with second-order in the spinal cord's dorsal horn. Low activity levels are encoded in innocuous stimuli, and high levels are encoded in noxious stimuli.
Pain pattern	It posits that the organs of the somatic senses respond to a dynamic range of stimulus intensities. The different organs of the senses have different levels of responsiveness to stimuli.
Pain control	The inhibitory effect of Rolando's gelatinous substance on afferent fibres in central transmission cells increases with activity in type A fibres and decreases with activity in type C fibres.

One common approach to grading pain using neuroimaging is to measure the amplitude and extent of brain activity in pain-related brain regions in response to noxious stimuli. Brain activity can be measured using imaging techniques such as fMRI, PET, and magnetoencephalography (MEG). The resulting data can then be used to develop a quantitative measure of pain intensity, such as a score [39]. However, there are several existing problems with using neuroimaging to grade pain. One challenge is the variability in pain perception and response across individuals [40]. Pain perception is influenced by various factors, including genetic, environmental, and psychological factors, and there is significant variability in how individuals perceive and respond to pain. This variability can make it difficult to develop reliable and objective measures of pain using neuroimaging. Another challenge is the complexity of pain perception and processing in the brain. Developing a comprehensive understanding of pain processing in the brain and developing reliable measures of pain grading will require a more nuanced understanding of the complexity of pain perception and processing [41]. Finally, ethical concerns are associated with using neuroimaging to assess pain, particularly in vulnerable populations such as children or individuals with cognitive impairments. It is crucial to ensure that any use of neuroimaging to grade pain is done ethically and responsibly, with proper consideration given to consent, privacy, and confidentiality issues.

6. PAIN PERCEPTION THEORIES

Various approaches have been postulated to describe the underlying mechanisms of pain perception, such as the theory of the specificity of pain, the method of grading pain intensity, pain patterns, and the approaches for pain control [42, 43]. The perception of pain occurs in two phases: the initial one after the acute stimulus (where the pain is not particularly intense), known as *rapid pain,* and a later one, known as *slow pain* (where it is a more unpleasant, localised, long-lasting period and accompanied by emotional, psychological disturbances anticipating pain duration) [44]. Table **5** summarises the four main theories related to pain perception.

6.1. The Neural Process of the Pain Signal

This process begins with transduction, the process by which the nociceptive stimulus is converted into an electrical signal in the nociceptors. The nociceptors respond to different thermal, mechanical, or chemical harmful but do not react to non-nociceptive stimuli [45]. Peripheral neurotransmitter release allows the classic "reflex axon," which causes peripheral changes recognised as pain indicators: redness and volume increase. The pain results from the activation of the peripheral nociceptors by the release of neurotransmitters and by the decrease in the response threshold of the nociceptive fibres. When there is tissue damage, the "silent" nociceptors are recruited, responding to stimuli. When sensitising nociceptors, the response may be more vigorous, leading to hyperalgesia. Opioid receptors located in the peripheral nerve endings, when activated by endogenous or exogenous opioids, inhibit the afferent impulse [46].

The second stage of the nociceptive signal is transmission: information from the periphery to the spinal cord, the thalamus, and the cerebral cortex. The data is transmitted through two primary afferent nociceptive neurons. The spinothalamic tract is the most important pathway for the rise of afferent pain signals from the spinal cord to the cortex. It is subdivided into neo-spinothalamic and paleospinothalamic. The rapid pain signal's neo-spinothalamic impulse is the primary pathway that discriminates the different aspects of pain: location, intensity, and duration. The paleospinothalamic beam transmits slow, chronic pain; the unpleasant emotional perception travels this way; substance P is the most critical neurotransmitter. The second-order neurons in the dorsal horn of the spinal cord can change their response pattern in circumstances of sustained discharge of the afferent fibres phenomenon known as "sensitisation". Central sensitisation "contributes" o the phenomenon of hyperalgesia and allodynia [47]. Later, brain interpretation occurs where the thalamus analyses most nociceptive stimuli, which follow the cerebral cortex when the insula receives input from SI, SII, pulvinar, central median, and parafascicular nuclei, and medial dorsal nucleus. It demonstrates a graded response proportional to the intensity of the noxious stimulus and is likely involved in the sensory-discriminative processing of pain [48].

6.2. Descending Modulator System

Activation of the descending system by endorphins occurs through opioids specific receptors. This system is activated around the periaqueductal grey matter of the mesencephalon, inducing inhibition of the dorsal horn neurons [49]. These neurons project to the reticular medullary formation and the locus coeruleus, where serotonin and norepinephrine are produced [50]. The descending fibres are then projected to the dorsolateral funiculus of the dorsal horn of the spinal cord for the synapse with the primary afferent neuron. Descending pain

modulator neurons have the following functions: serotonin-norepinephrine releases neurotransmitters in the spinal cord. Activate interneurons that release opioids in the spinal dorsal horn.

6.3. Inhibition of the Second Cell Order in the Transmission of Pain

The administration of opioids results in activating opioid receptors in the mesencephalon. Activating opioid receptors in pain-transmitting second-order cells prevents the upward transmission of the pain signal [51]. Activation of opioid receptors in the central terminals of C-fibers in the spinal cord prevents pain neurotransmitters. It activates opioid receptors in the periphery to inhibit the trigger of nociceptors and inhibit cells that release inflammatory mediators. With the PET technique, activation of the ventral anterior and lateral thalamic nuclei has been observed, which are about the motor cortex and could explain the effect on movement disorders. Increased blood flow of structures involved in pain control has also been observed: medial thalamic nuclei, cingulate gyrus, insula, and upper trunk. These structures seem to be involved in the modulation of pain. Another mechanism proposed is a "gate-control" effect due to the downward inhibitory action of the pyramidal beam on the posterior horn [52 - 54].

A systematic review and meta-analysis of opioid-induced hyperalgesia (OIH) in patients following surgery [55] published the incidence and severity of OIH in patients receiving opioids for postoperative pain management. The review included 34 studies involving over 1500 patients and found that OIH was relatively common, with an overall incidence of around 12%. The authors also found that the severity of OIH was positively correlated with the dose and duration of opioid exposure and with specific patient characteristics such as age and sex.

The mechanism of OIH through NMDAr involves the activation of *N*-methyl-*D*-aspartate receptors (NMDAr) in the dorsal horn of the spinal cord. Chronic exposure to opioids leads to an increase in the activity of the NMDAr, resulting in increased neuronal excitability and sensitisation of pain pathways. This sensitisation leads to a reduced threshold for pain and an increased response to painful stimuli, resulting in hyperalgesia. The interaction between opioids and NMDAr is complex, with opioids acting as NMDAr antagonists under certain conditions and NMDAr agonists under others. The net effect of chronic opioid exposure is an upregulation of NMDAr, leading to an overall increase in NMDAr activity and hyperalgesia [56]. The mechanisms underlying OIH through NMDAr are still under investigation, and further research is needed to understand fully. Preventing OIH requires a proactive approach to pain management that considers the risks and benefits of opioid use and alternative strategies for pain management, avoiding long-term or high-dose opioid use, considering alternative pain management strategies, rotating opioid medications, and using multimodal analgesia [57]. In 2020, Tognoli and Cols [58] published a randomised controlled trial to compare the analgesic efficacy of methadone with that of morphine in patients undergoing major abdominal surgery. They found that methadone provided superior analgesia to morphine, with a longer duration of action and reduced opioid consumption. The authors attribute this to the NMDAr antagonism of methadone, which has been shown to reduce the development of opioid tolerance and hyperalgesia. The potential benefits of methadone in postoperative pain management, particularly in reducing the risk of opioid-induced hyperalgesia and the need for high doses of opioids, may be a valuable alternative to traditional opioids in this setting.

7. DISCUSSION

Pain is a complex and subjective experience that can be influenced by various factors such as genetics, environment, and emotional state [59]. The sensation of pain is initiated by activating nociceptors, specialised sensory receptors that respond to noxious stimuli, such as heat, cold, or mechanical pressure. These nociceptors, including the skin, muscles, and organs, are throughout the body.

Once activated, nociceptors send signals through nerve fibres, eventually reaching the spinal cord. The spinal cord is a relay station transmitting pain signals to the brain. From the spinal cord, the pain signals travel through ascending pathways to reach the brain, where they are processed and interpreted.

The thalamus is an important relay station in the brain that receives sensory information from the spinal cord and relays it to the appropriate brain regions. The somatosensory cortex processes touch, temperature, and pain information. The insula is involved in the emotional aspects of pain perception, such as the unpleasantness or suffering associated with pain. The anterior cingulate cortex is involved in the cognitive aspects of pain perception, such as attention, decision-making, and motivation. Finally, the prefrontal cortex is involved in the modulation of pain perception and can influence the intensity and unpleasantness of the pain experience.

Neuroimaging techniques such as fMRI and PET have been used to study the neural mechanisms underlying pain perception. These techniques allow us to visualise changes in brain activity associated with pain experience [60].

One of the key findings from neuroimaging studies of pain is that pain perception is not simply a result of the activation of a single brain region but rather a complex network of brain regions that work together to create the experience of pain. For example, studies have shown that the placebo effect, in which a person experiences pain relief from a sham treatment, is associated with changes in brain activity in the prefrontal cortex and other regions involved in pain processing [61]. These findings highlight the importance of psychological and emotional factors in pain perception and suggest that psychological interventions, such as cognitive-behavioural therapy, may effectively reduce pain perception [59].

Neuroimaging studies have led to the development of new treatments for pain that target specific brain regions involved in pain perception. For example, transcranial magnetic stimulation (TMS) is a non-invasive technique that uses magnetic fields to stimulate particular brain regions. TMS has been used to target the prefrontal cortex and other brain regions involved in pain processing, with promising results in reducing pain perception [62].

The knowledge of the pathways of pain undoubtedly leads us to clinical use. Since more in-depth knowledge allows the study and development of drugs focused on different receptors and treatment techniques that have resurfaced, such as psychosurgery, this subspecialty of functional neurosurgery has been used to treat psychiatric diseases, intractable pains and neurological syndromes that cause chronic pain [63]. These techniques have led to several key findings that have greatly enhanced our understanding of pain pathways and have important implications for treating pain.

After reviewing the anatomy and physiology of pain, we can comment on our surgical options today. There are several lesion techniques and neuromodulation. Of the first, we can name peripheral neurectomy, rhizotomy and ganglionectomy, sympathectomy, dorsal root entry zone lesion (DREZ), chordotomy, myelotomy, trigeminal pontine lesion, mesencephalotomy, subcortical lesions. Of the latter, we can comment on transcutaneous magnetic neurostimulation, peripheral nerve stimulation, chronic analgesic spinal cord stimulation, analgesic deep brain stimulation, and analgesic cortical motor stimulation. Some are still used, and others are in disuse.

Percutaneous neurotomy is no longer used because of the side effects it causes. Rhizotomy has as primary indications cancer pain, suboccipital neuralgia or postoperative low back pain syndrome [64].

Sympathectomy may be an option in causalgia, reflex sympathetic dystrophy, or ischemic vascular disorders. DREZotomy is used in patients with cancer pain, brachial plexus avulsion, incomplete spinal cord injuries, and postherpetic neuralgia [65]. Cordotomy is used in cancer pain, mainly in the pelvis or lower limbs [66]. Myelotomy may be used in cancer pain when the pain is bilateral on the pelvis [67]. Trigeminal tractotomy, nucleotomy, or DREZotomy is used for patients with orofacial cancer pain or orofacial deafferentation pain [68]. Medial thalamotomy has been used for orofacial pain and cancer pain. Cingulotomy is used to improve the affective component of pain [69]. Hypophysectomy has been resumed and is used in patients with cancer pain [70].

For example, trigeminal neuralgia is a chronic neuropathic facial pain disorder commonly responding to surgery [71]. A proportion of patients, however, do not benefit and suffer continuous pain; for example, trigeminal neuralgia originates from a trigeminal vascular compression by a vascular curl or a tumour in the cerebellar angle and responds very well to microvascular decompression and other procedures such as percutaneous rhizotomy and balloon compression of the Gasser ganglion [74]. Currently, imaging tools predict the response to treatment, reduction by a vascular curl in the pontocerebellar angle evidenced by MRI [73]. However, multisensory tractography indicates the surgical response [74]. New technology and knowledge of pain have provided greater accuracy with less morbidity. The progressive replacement of ablation procedures with deep brain stimulation and restorative neurosurgery offers new perspectives in treating these conditions [75]. The application does not end there. Carrying out a blockade to decrease the inflammatory response and "turn off" the signal that causes pain and a specific distribution of nerves guided by imaging techniques also allows maximum benefit [76]. Fig. (**10**) exemplifies the relationships between neuroanatomy, neurophysiology, and neuroimaging with current treatment options.

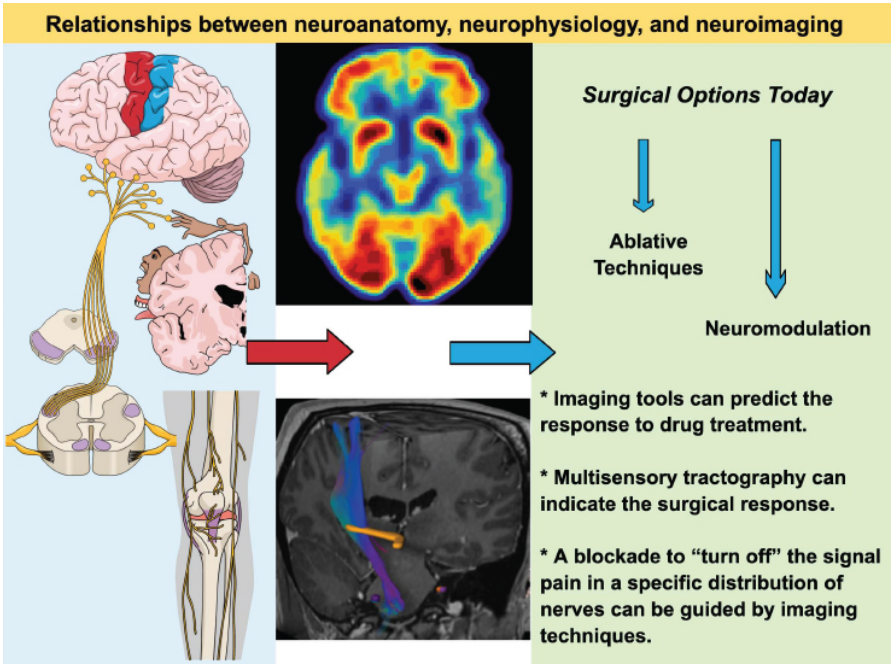

Fig. (10). Relationships between neuroanatomy, neurophysiology & neuroimaging.

8. FUTURE DIRECTIONS

Future directions of pain pathways research include further elucidation of the molecular and cellular mechanisms involved in pain processing, particularly in the peripheral nervous system. This may involve a greater focus on studying the role of immune cells, glia, and other non-neuronal cells in pain initiation and maintenance [77]. There is also a need for more research on the interplay between different pain pathways, such as the interaction between nociceptive and neuropathic pain.

Another critical area of future research is the development of new therapies for chronic pain that target specific components of the pain pathway. For example, there is growing interest in using gene therapy and RNA-based therapies to treat chronic pain [78]. Additionally, there is a need to improve our understanding of the impact of environmental and social factors on pain perception and to develop more effective interventions to address the psychological and emotional aspects of chronic pain [62].

Advancements in neuroimaging techniques such as ultra-high field MRI, optogenetics, and advanced EEG and MEG approaches are also expected to contribute significantly to our understanding of pain pathways. However, these functional aspects need to be connected with the foundations of morphologic anatomy; for example, it is currently known the specific volumes of brain gyri and even the asymmetry indices that identify structures in cerebral hemispheres [79]; another challenge is understanding the existing variation between pain pathways connectivity with gender, and cerebral hemisphere variations in basal ganglia, as it was studied a decade ago but in volumetric studies [80]. These techniques can potentially provide unprecedented spatial and temporal resolution of neural activity, which can help identify novel pain therapy targets and improve existing treatments' efficacy; recent studies, for example, have demonstrated the plasticity of neural networks after umbilical cord blood cells therapy in patients with schizophrenia [81, 82]; and the selection of specific pre lemniscal thalamic radiations as a target for the treatment of Parkinson disease [83]; these are examples of pathologies with altered pain perception. Current research lines related to pain pathways involve a wide range of categories, including specific pathologies such as mechanisms underlying chronic pain [84], genetics of pain [85], and the development of novel pain therapies [86].

CONCLUSION

In conclusion, neuroimaging studies have significantly advanced our understanding of the neural mechanisms underlying pain perception. These studies have shown that pain is a complex and subjective experience that involves a network of brain regions working together to create the pain experience. These studies have highlighted the importance of expectations, attention, and emotional state in influencing pain perception.

Neuroimaging techniques such as fMRI, PET, and BOLD have revolutionised our understanding of the neural mechanisms underlying pain perception and modulation. Moreover, neuroimaging has also been instrumental in understanding the impact of cognitive and emotional factors on pain perception and how these factors can modulate the pain experience. Additionally, neuroimaging has been used to develop and evaluate new treatments for pain, such as TMS intervention.

The importance of pain pathways and their association with neuroimaging techniques cannot be overstated. They have allowed us to understand better the complexity of pain and the subjective nature of pain perception. The insights provided by neuroimaging studies have paved the way for developing more effective and targeted pain treatments, which can potentially improve the quality of life for millions of people suffering from chronic pain.

Despite more than 50 years of research about the pain pathway, the increasing numbers of studies in recent years tell us that the role of functional imaging will continue growing for many years. In a few years, we believe that we will be able to predict the decrement of pain in selected diseases, understand the severity progression in some cases, and find a balance in the cost-benefit of the imaging modalities.

LIST OF ABBREVIATIONS

ACC	=	Anterior Cingulate Cortex
ASL	=	Arterial Spin Labelling
BOLD	=	Blood Oxygenation Level-dependent
cAMP	=	Adenosine Cyclic Monophosphate
CNS	=	Central Nervous System
DH	=	Dorsal Horn
DREZotomy	=	The Dorsal Root Entry Zone Section
DRG	=	Dorsal Root Ganglion
fMRI	=	Functional Magnetic Resonance Imaging
MEG	=	Magnetoencephalography
MITN	=	Intralaminar Thalamic Nuclei
NMDAr	=	N-methyl-D-aspartate Receptors
OIH	=	Opioid-induced Hyperalgesia
PAG	=	Periaqueductal Grey Matter
PET	=	Positron Emission Tomography
Vcpc	=	Ventralis Caudalis Parvocellularis
VPL	=	Ventral Posterolateral Nuclei
VPM	=	Ventral Posteromedial Nuclei

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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