Physiopathology of Pain

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Serge Marchand

Abstract

The different brain imaging techniques that have emerged in the last decades have raised major advancement in our understanding of the neurophysiological mechanisms implicated in pain in both healthy subjects and in patients suffering from different pain conditions. The new brain imaging protocols are developed based on the background of previous surgical, behavioral, psychophysical, and electrophysiological researches on nociception and pain in animal, healthy subject, and patients. Having a good background of normal and pathophysiological pain neurophysiology is essential for the design of research protocols that will take advantage of new brain imaging technologies to better investigate the complex phenomenon of pain. Pain is a dynamic phenomenon that is the end result of several factors. The association between nociceptive activity and pain perception depends on several intrinsic and extrinsic influences. For the same nociceptive stimulus, pain perception and related brain activity will greatly differ between subjects. Studies support that environment and genetic factors are both playing important roles and seem to be modality specific. The effect of environment on genetics, epigenetics (lasting changes in gene expression without alteration of DNA sequence), is essential to be taken into account in pain. Nerve injuries or even psychological factors could change the central nervous system by affecting DNA methylation and produce a "genomic" memory of pain in the adult cortex. Pain perception is then the result of inherited physiological and psychological factors that are influenced by and hopefully guide the development of new therapeutic approaches for the patients that are suffering.

S. Marchand (✉)
Department of Surgery/Division of Neurosurgery,
Université de Sherbrooke, Sherbrooke, Québec,
Canada
e-mail: Serge.Marchand@USherbrooke.ca

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1 Introduction

The different brain imaging techniques that have emerged in the last decades have raised major advancement in our understanding of the neurophysiological mechanisms implicated in pain in both healthy subjects and in patients suffering from different pain conditions.

The new brain imaging protocols are developed based on the background of previous surgical, behavioral, psychophysical, and electrophysiological researches on nociception and pain in animal, healthy subject, and patients. Having a good background of normal and pathophysiological pain neurophysiology is essential for the design of research protocols that will take advantage of new brain imaging technologies to better investigate the complex phenomenon of pain.

Pain is a dynamic phenomenon that is the end result of several factors. The association between nociceptive activity and pain perception depends on several intrinsic and extrinsic influences. For the same nociceptive stimulus, pain perception and related brain activity will greatly differ between subjects. Using functional magnetic resonance imaging (fMRI) of the brain, Coghill and colleagues found that the more sensitive subjects exhibited more pain-induced activity in the primary somatosensory cortex, anterior cingulate cortex (ACC), and prefrontal cortex (PFC) than did less sensitive subjects [11]. Interestingly, they also found that the thalamus activity was not different between the two groups, supporting that the same nociceptive signal is transported to the thalamus. It is the sensory and affective pain-related brain structures that are encoding for these inter-individual differences in pain perception.

The importance of intrinsic factors in pain is supported by genetic predispositions to be less or more sensitive to pain [91]. In one study comparing 59 identical pair of twins with 39 fraternal twins, the authors conclude that 60% of the variance in cold pressor pain and 26% of the variance in heat pain was genetically mediated [60]. These results suggest that environment and genetic factors are both playing important roles and seem to be modality specific. The effect of environment on genetics, epigenetics (lasting changes in gene expression without alteration of DNA sequence), is also essential to be taken into account in pain [6]. Nerve injuries or even psychological factors could change the central nervous system by affecting DNA methylation and produce a "genomic" memory of pain in the adult cortex [21]. It could even explain the comorbidity between some psychiatric factors such as depression and pain [76]. These results support the importance of psychological factors such as mood, anxiety, catastrophizing, and personality in pain perception [84].

Pain perception is then the result of inherited physiological and psychological factors that are influenced by our environment. Together these factors are framing our reaction to different painful situations, but probably also our predisposition for pain chronification.

2 Theories of Pain Mechanisms

Researches are driven by theories. Most of the time we need a challenging new paradigm to emerge to stimulate new research protocols that will lead to new theories. The clinical approaches for the treatment of pain are based on these theories. It is then interesting to have a brief

overview of the evolution of our understanding of pain mechanisms. It helps us realize that the evolution of pain treatments is highly related to motley of older and new pain theories to explain pain mechanisms.

2.1 Specificity Theory

The specificity theory was first introduced by Descartes during the seventeenth century [22] and refined with the modern physiology by Müller [59] and Frey [28] at the end of the nineteenth century. They proposed that the somatosensory system could be divided according to specific receptors for tactile, hot, cold, and pain receptors. With the specificity, we have a theoretical framework to explain how specific afferences from the periphery, Aδ and C fibers, are connecting to specific pathways, spinothalamic, and spinoreticular tracts from the spinal cord, that are sending their fibers to specific structures of the thalamus, ventrolateral, and ventromedian nuclei, to cortical structures that are related to sensory, primary and secondary somatosensory cortices, and affective, anterior cingulate and insular cortices, components of pain [9].

The specificity theory is still confirmed by the identification of specific receptors, fibers, pathways, and CNS structures that are responsible for our perception of these somatosensory modalities. Even if several studies are supporting that these pathways and higher center structures are definitely playing a role in pain perception, their anatomical identification is not sufficient to explain the complexity of pain. The mechanisms involved in different conditions, such as the increasing perception of pain following repetitive nociceptive stimuli (temporal summation) or of a larger surface (spatial summation) or some chronic pain conditions, clearly support that the specificity theory alone cannot explain the complexity of pain.

2.2 Pattern Theory

The pattern theory, introduced by Goldscheider [30], suggested that not only the type of fibers, the pathways, or the different anatomical structures but also the pattern of impulses in the nervous system would modulate pain perception. Based on this theory, it is easier to understand that a thermal stimulus can pass from a warm perception to burning hot if the stimulation persists at the same temperature (temporal summation) or is presented on a larger surface (spatial summation).

Changes in the activation patterns could help understand complex phenomenon such as allodynia, pain from a non-painful stimulus, or spontaneous pain in conditions where no apparent lesions are detectable. We understand that even small changes in the neuronal activity of spinal or supraspinal structures will be sufficient to produce what is now known as central sensitization. Central sensitization can be described as a plasticity of the central nervous system that will produce a reduction of the threshold to produce a painful sensation to the point that even a non-nociceptive stimulus will be perceived as painful (allodynia) or more painful than usual (hyperalgesia) and a receptive field expansion that will enable the non-injured tissue to produce pain (secondary hyperalgesia) [95].

2.2.1 Patterns and Brain Dynamics

Electroencephalographic (EEG) activity of pain perception revealed that synchronous gamma-band frequency (30–100 Hz) seems to play a major role in the cortical integration of multiple sensory modalities, including pain [50]. Because of their non-specific modality responses, it was suggested that gamma-band oscillation (GBO) is more related to salience or attention [37]. However, primary somatosensory cortex (S1) GBO is correlating to pain perception, even when salience is reduced by repetition [100]. These results on GBO and other recent pain imaging techniques are stressing out that activity patterns and not just anatomical locations are essential to render the complexity of pain perception.

2.3 Gate Control Theory

In 1965 the gate control theory by Melzack and Wall [56] came with another important part of

the complex puzzle of pain: the fact that endogenous pain modulatory mechanisms could enhance or reduce pain perception. For instance, the gate control theory proposed that the stimulation of non-painful Aβ afferences could produce a localized analgesia by blocking the nociceptive afferences directly at their entry in the spinal cord. Moreover, even if the specific mechanisms were not explained in the gate control theory, Melzack and Wall already proposed that descending mechanisms from higher centers would influence this modulatory mechanism.

2.4 Diffuse Noxious Inhibitory Mechanisms

A few years after the gate control theory was proposed, Reynolds demonstrated that stimulation of the periaqueductal gray (PAG) in the brainstem produced a strong inhibition [69]. The role of the rostroventral medulla in the modulation of pain has since been well documented [25]. Regions such as the PAG and the nucleus raphe magnus (NRM) have been identified as important serotoninergic and noradrenergic descending inhibitory pathways. These inhibitory pathways then recruit enkephalinergic interneurons in the spinal cord to produce the analgesic response.

We had to wait until the end of the 70s before a model known as diffuse noxious inhibitory controls (DNIC) was proposed [48, 49]. This model is based on the observation that a localized nociceptive stimulation can produce a diffuse analgesic effect over the rest of the body, an analgesic approach known as counter-irritation. In the DNIC model, Le Bars et al. [48, 49] proposed that a nociceptive stimulus will send input to superior centers, but will also send afferences to the PAG and NRM of the brainstem, recruiting diffuse descending inhibitory output at all levels of the spinal cord.

Together, the gate control and DNIC have played a very important role in supporting that pain perception is not only the endpoint of nociceptive activations but will also be modulated by several endogenous mechanisms. Deficits of these mechanisms are probably responsible for several complex chronic pain conditions [98].

2.5 Pain as a Homeostatic Emotion

Another very interesting view of pain has been proposed by Bud Craig [14]. Rather than seeing pain as part of the exteroceptive sense of touch, he suggests that we have neuroanatomical and neurophysiological demonstrations that it is in fact a homeostatic signal. The human feeling of pain is then both a distinct sensation and a motivation at the same time. This model makes sense when we think that pain is described as a sensory, affective, and cognitive experience. Moreover, even the International Association for the Study of Pain (IASP) is describing pain as the result of an actual or potential lesion. All these descriptions are fitting homeostatic behavioral drives. Moreover, lesion of the somatosensory cortex is not affecting pain, while thalamic stimulations are producing analgesia [14]. The earliest brain activity following a nociceptive stimulus is in the posterior insula and mid-cingulate cortex [51], two regions that are playing a role in the affective reactions and in homeostasis.

3 From the Periphery to the Cortex

One approach to study the neurophysiology of pain is to follow the nociceptive signal from the periphery to the cortex. It is also important to appreciate the role of descending signal from the higher centers to the brainstem and periphery that will modulate the nociceptive signal at all the level of the central nervous system, changing our pain perception.

There is no direct relation between nociceptive activity and pain perception. The term “nociception” comes from Sherrington’s observations regarding stimuli that are likely to affect the integrity of the organism [72]. It indicates potentially painful or algesic nerve information

before it comes to consciousness or higher brain centers. Frequently a nociceptive stimulus will be translated in pain; however, several conditions can change this perception depending on the salience or significance of the information that reach consciousness at the same time [90]. In a neutral condition, pain is normally very salient. It is a protective mechanism. However, in an emergency situation or during an important distraction, pain salience may shift to a second order and will be felt as lower or even absent.

In Fig. 1, we can follow the nociceptive signal from the periphery to the cortex.

(1) The nociceptive signal (mechanical, chemical, or thermal) will recruit peripheral nociceptors that conduct the signal in the primary afferent neurons to the dorsal horn of the spinal cord.
(2) In the dorsal horn, the primary afferent neuron will make a synaptic contact with the secondary or projection neuron that will constitute the spinothalamic and spinoreticular tracts that immediately cross in the spinal cord and send contralateral afferent projections to higher centers.
(3) A large proportion of afferents will make a second synapse in the lateral and medial nuclei of the thalamus. **It is important to emphasize that the secondary neurons may also synapse with neurons in different nuclei of the brainstem including the PAG and the NRM, areas involved in descending endogenous pain modulation.
(4) From the thalamus and brainstem nuclei, the secondary neuron will project to tertiary neurons to the primary and secondary somatosensory cortices (SI, SII). The SI and SII are involved in the sensory quality of pain, which includes location, duration and intensity. Tertiary neurons also project to limbic structures, including the ACC and the insula, which are involved in the affective or emotional component of pain.

All synaptic contacts with excitatory and inhibitory neurons at all levels of the CNS are site of important integration regions that are the target of most pharmacological approaches.

3.1 The Role of Glial Cells

During the last century, all efforts to understand the CNS mechanisms implicated in pain were focused on neurons. We just start to realize that glial cells are not just there for support or protection, but are playing a major and active role in several CNS processes, including pain [20]. The role of astrocytes [40] and microglia [75] have been well documented in the development and persistency of pain, especially in models of neuropathic pain. In normal conditions, glial cells seem to play a limited role in pain, with no or few effects on pain threshold [75]. However, after an injury, microglia becomes reactive. Activation of microglia in the dorsal horn is concomitant with the development of neuropathic pain [83]. Microglia releases several factors that are pronociceptive and mediated through a complex signaling system involving cytokines [96]. Even the paradoxical opioid-induced hyperalgesia phenomenon could be related to an action of microglial cells in the spinal cord [24]. Interestingly, there are several microglia-targeting drugs that can be developed based on the results from animal researches [75, 87, 96].

Imaging techniques using PET-MRI radiolabelling of glia activation markers are able to demonstrate the importance of glial activation in structures such as the thalamus in some chronic pain conditions [53].

We can no longer focus on the neurophysiology of pain without taking into account the major role of the glial cells and their roles in the development and treatment of pain.

3.2 From the Periphery to the Spinal Cord

Even if imaging techniques are particularly aiming at the activity of the higher centers, it is important to remember what is happening from

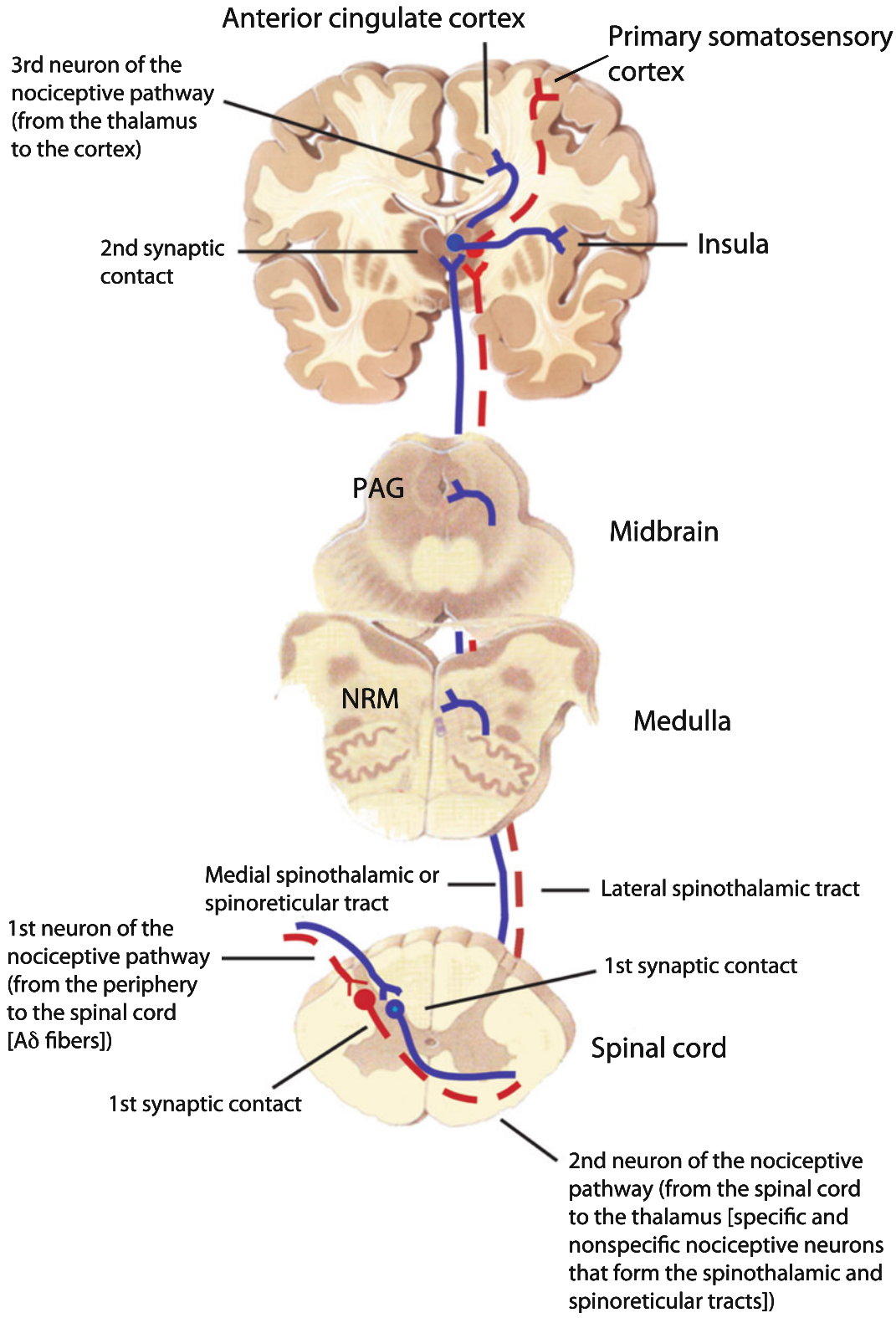
Anterior cingulate cortex
Primary somatosensory cortex
3rd neuron of the nociceptive pathway (from the thalamus to the cortex)
2nd synaptic contact
Insula
PAG
Midbrain
NRM
Medulla
Medial spinothalamic or spinoreticular tract
Lateral spinothalamic tract
1st neuron of the nociceptive pathway (from the periphery to the spinal cord [Aδ fibers])
1st synaptic contact
Spinal cord
1st synaptic contact
2nd neuron of the nociceptive pathway (from the spinal cord to the thalamus [specific and nonspecific nociceptive neurons that form the spinothalamic and spinoreticular tracts])

Fig. 1 Pain pathways: From the periphery to the cortex, we can follow the lateral spinothalamic (*broken red line*) and the spinoreticular (*full line*) from the periphery to the cortex. The lateral spinothalamic tract is projecting to the lateral thalamus nuclei and to the somatosensory cortex. The spinoreticular tract is projecting to the medial thalamus and different cortical structures associated to the affective component of pain including, but not restricted to, the insula and the cingulate cortex. These different pain pathways are activating the brain structures responsible for the complex pain-related perception

the periphery to make sense of what we found at the spinal and supraspinal level.

Afferent fibers originating in the periphery fall into three groups, namely Aβ, Aδ and C fibers.

3.2.1 Non-nociceptive Afferent Fibers

The Aβ fibers are large myelinated fibers that conduct at high speed (35–75 m/s) and usually transmit non-nociceptive signals. They do however also participate in pain modulation by recruiting inhibitory interneurons in the *substantia gelatinosa* of the dorsal horn of the spinal cord. This mechanism is one of the fundamental components of the gate control theory, whereby an innocuous stimulus will reduce the nociceptive input from the same region [56]. Besides playing a dynamic inhibitory role when recruited, the Aβ fibers seem also to play a tonic inhibitory role on the nociceptive input. Blocking the input from these large fibers will result in an increased response to nociceptive stimuli [67].

3.2.2 Nociceptive Fibers

Two other classes of fibers, the myelinated Aδ and the thin unmyelinated C fibers mainly transmit nociceptive messages. The Aδ fibers are myelinated and relatively large, conducting the signal relatively rapidly (5–30 m/s) from the periphery to the spinal cord. Because of this rapid conduction velocity, they are responsible for the sharp localization of pain and for the rapid spinal response, which can be measured in the laboratory as the nociceptive reflex. They represent the majority of the myelinated fibers. Two types of Aδ fibers exist depending on the specificity of their responses to different stimulation [8]: (1) the mechanonociceptors respond preferentially to intense and potentially harmful mechanical stimulation; and (2) the polymodal Aδ fibers respond to mechanical, thermal and chemical stimulations. Because of the rapid conduction velocity, the Aδ fibers are responsible for the first pain sensation, a rapid pinprick-like, sharp and transient sensation.

In contrast, the C fibers that have a slow conducting velocity (0.5–2 m/s) will mediate a second or dull aching pain. They represent three quarters of the sensory afferent input and are mostly recruited by nociceptive stimulation. Because of their slow conduction velocity, they are responsible for the second pain, a dull, diffuse and late sensation. However, they are also involved in non-nociceptive somatosensory information such as in the sensation of itch (pruritus) [74], and paradoxically, in the perception of pleasant touch, as documented in a patient with a rare disease linked to a deafferentation of the myelinated sensory fibers [62]!

3.2.3 First and Second Pain

The conduction velocity differences between the Aδ and C fibers can be appreciated when isolating the sensation of first and second pain (Fig. 2). Following a brief nociceptive stimulation, the Aδ fibers will rapidly transmit a brief and acute pinprick-like sensation perceived to be precisely located at the point of stimulation. Following this activity, C fibers will transmit their information, with a relatively long delay (100 ms to a second depending on the stimulus location). This second sensory input results in a more diffuse deep pain sensation.

It is possible to isolate first and second pain in the laboratory. Using a blood pressure cuff, we can temporarily block trophic factors present in the blood from reaching the nerves, resulting in a reduction of nerve conduction. The first fibers that will show reduced activity are those with largest diameter, including the Aδ fibers. This allows the activity of C fibers to be isolated and independently studied. Following this procedure, a nociceptive stimulation, independent of the nature of the stimulation, hot, cold or mechanical, will be perceived with a certain delay as a deeper pain sensation.

The application of capsaicin, the hot pepper extract, will produce a burning sensation due to the activation of the vanilloid receptors on C fibers. However, at higher doses, C fibers will be blocked as a result of a specific action on calcium ion channels, with resulting isolation of the Aδ fibers at the skin surface. This time, the same nociceptive sensation will be perceived as a sharp pinprick-like sensation without the second burning pain sensation.

Cortical representation of first and second pain has also been studied using magnetoencephalography (MEG). Among the regions activated, first pain was particularly related to activation of S1 whereas second pain was closely related to anterior cingulate cortex activation [66]. However, another study found no specific activations, but proposed that it's rather the recruitment of the same structures with different time windows.

3.3 The Spinal Cord: First and Important Step in the Central Nervous System

The first major distinction between nociceptive and non-nociceptive afferent fibers is that the latter ascend ipsilaterally (on the same side) to the brainstem before making synaptic contact with the second neuron and finally crossing to the opposite side before projecting to higher centers. For nociceptive fibers, the signal is transported to the dorsal horns of the spinal cord (or the brainstem for trigeminal afferent impulses) to make first synaptic contact with the secondary neurons (or projection neurons). The secondary neurons cross the spinal cord immediately under the central canal to form the spinothalamic contralateral projection tract.

The Aδ and C nociceptive fibers occupy the ventrolateral position in relation to the dorsal root. They make their way through Lissauer's tract, upward or downward, along one or more segments. Then, they ipsilaterally penetrate the dorsolateral portion of the dorsal horn.

3.3.1 Organization of the Spinal Cord

The gray matter of the spinal cord is divided into 10 cytoarchitectonic layers or laminae (known as Rexed laminae). The Aδ fibers mainly end in the first lamina and in the superficial portion of the second. Afferent fibers coming from the deep tissue and viscera, on the other hand, essentially end in laminae I and V [57]. C fibers mainly end in laminae I and II. As for the large myelinated Aβ fibers, they complete their journey in lamina III or deeper. In spite of their characteristic entry into the laminae, Aβ, Aδ, and C fibers establish connections among one another. The dorsal horn remains the preferred site for significant synaptic convergence. In fact, the same fiber from the dorsal horn of the spinal cord can receive cutaneous, muscular, and visceral afferent impulses [47]. The convergence of afferent impulses originating from different systems allows us to better understand the interaction that can exists between systems that seem independent at first. Therefore, muscular pain could be exacerbated by a new visceral pain, and vice versa.

The dorsal horns contain an important network of synaptic convergences, bringing together the collateral fibers and interneurons. Thus, passage through the sensory spine is an important step during which nociceptive information will be modulated. Its complex network of neurons, which includes endings of primary nociceptive neurons, secondary neurons, interneurons, and neurons of descending tracts, contains a multitude of neurotransmitters and a sizeable mosaic of receptors that will modulate the nociceptive afferent impulses before they are forwarded to the higher centers.

Three main categories of nerve cells in the CNS participate in nociception: nociceptive projection neurons, excitatory interneurons, and inhibitory interneurons.

3.3.2 Projection Neurons

Nociceptive projection neurons relay the message to the higher centers and are classified into two groups: specific nociceptive projection neurons and multireceptive projection neurons [32, 78]. Specific nociceptive neurons are neurons

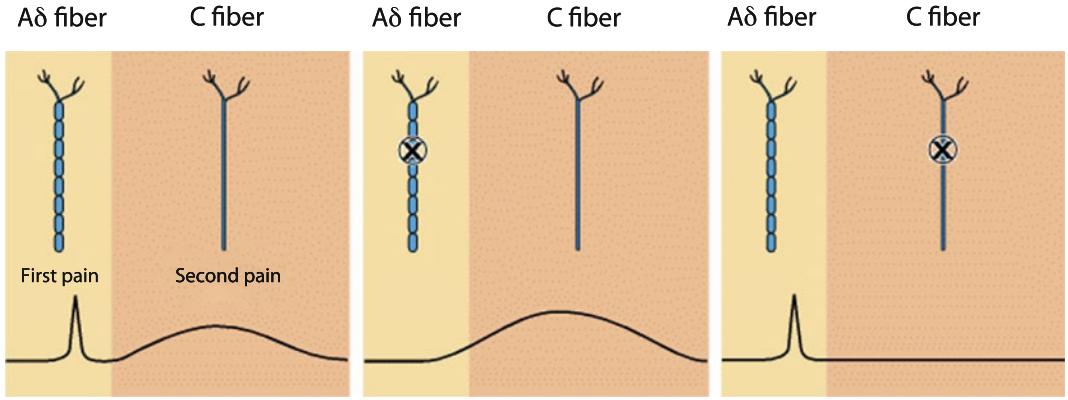

Fig. 2 Aβ, Aδ and C fibers

that receive their information only from primary afferent nociceptors. Therefore, they only respond to stimulations of mechanical or thermal origin of potentially painful intensity [2].

Multireceptive or wide-dynamic-range neurons gather information provided by the primary afferent nociceptors with mechanoreceptors. These are the neurons with small receptive fields that receive afferent impulses from Aδ and C fibers, and also from non-nociceptive Aβ fibers. Thus, these neurons of the dorsal horns of the spine respond in a graduated manner to stimulation of different intensity varying from non-nociceptive to nociceptive. Multireceptive neurons are dynamic and their receptive fields not only include excitatory area, but also inhibitory ones. Modification of these receptive fields plays an active role in certain types of chronic pain [47].

3.3.3 Pain Modulation in the Spinal Cord

An important challenge in pain imaging is to differentiate the signal from excitatory and inhibitory interneurons. The transmission of a nociceptive impulse is not summarized solely as the passage of nociceptive information between the first afferent neuron and the second projection neuron in the spinal cord. Excitatory and inhibitory interneurons actively participate in the modulation of nociceptive responses. As we saw a little earlier, glial cells also play a dominant role in nociceptive responses. The action of these excitatory and inhibitory neurons in spinal cord could lead to central sensitization, or hyperalgesia.

Hyperalgesia is defined as an exaggerated response to normally painful stimulation. In the 1950s, Hardy proposed that two kinds of hyperalgesia could affect the skin: primary hyperalgesia, occurring directly at the injury site, and secondary hyperalgesia, with its origins in the CNS [34]. Primary hyperalgesia can be explained by the release of different inflammatory factors in the periphery, which leads to the recruitment of nociceptors near the site of the injury (potassium, prostaglandins, bradykinin, histamine, substance P, and serotonin), which has the effect of recruiting nearby nociceptors and producing sensitization. The injury site as well as the neighboring tissues will thus have lower pain thresholds.

Secondary hyperalgesia, on the other hand, can be explained by a central phenomenon that is known by the general term "central sensitization" [95]. Repeated recruitment of C fibers after an injury can cause a series of events at the spinal level, which could have the effect of sensitizing the projection neurons in the dorsal horns of the spinal cord. High-frequency recruitment of C fibers will produce an increase in the action potential of the spinal neurons [23].

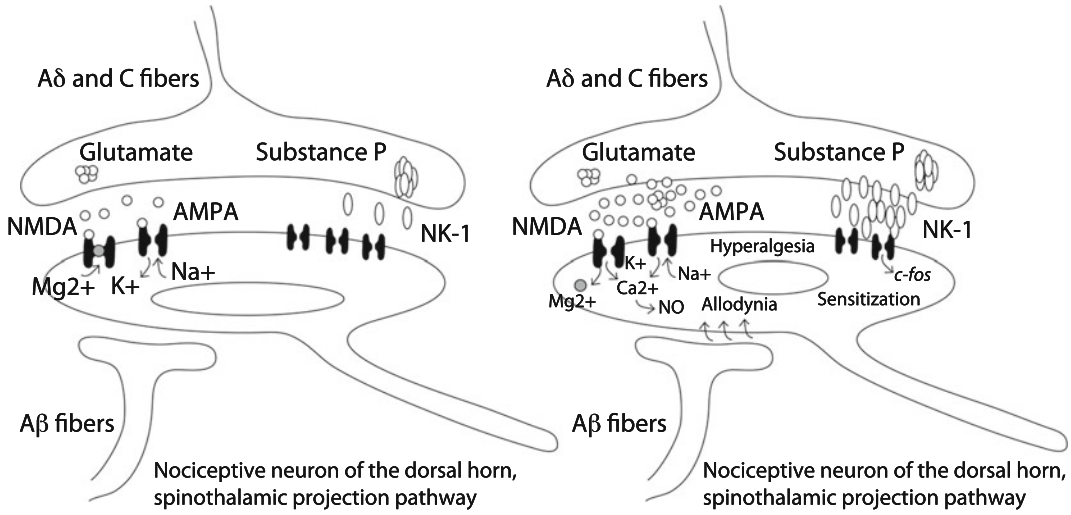

Fig. 3 Central sensitization: Following repetitive stimulation from a presynaptic neuron, high glutamate release will produce a cascade of postsynaptic activity that will produce long-lasting cellular sensitization resulting in central sensitization. Persisting central sensitization is proposed as being one the mechanisms implicated in chronic pain

Wind-up is a relatively short-lived transient phenomenon, but the repeated recruitment of C fibers can also lead to spinal sensitization, which may extend over several hours or even several days [86]. Thus, an intense, long-lasting stimulation will result in the recruitment of nociceptive fibers, including C fibers, which release excitatory amino acids (EAAs), glutamate, and peptides, such as substance P and CGRP. These neurotransmitters recruit postsynaptic glutamatergic receptors such as AMPA (α-amino-3--hydroxyl-5-methyl-4-isoxazole propionate) and NMDA in the case of EAAs, and neurokinin-1 receptors in the case of substance P. Prolonged stimulation of the NMDA receptors will produce long-lasting cellular sensitization through the activation of the gene transcription factors (c-fos and c-jun) (Fig. 3). These transcription factors induce the expression of some rapidly responding nuclear genes, in turn leading to nociceptor sensitization. This structural plasticity will have the effect of reducing the recruitment threshold of the nociceptors and thus producing hyperalgesia or allodynia, which could persist even after the injury has disappeared. The phenomenon of central sensitization allows us to better understand the importance of relieving pain as early as possible in order to avoid chronification.

3.4 Pain Pathways: From Spinal to Higher Centers

Generally, the nociceptive neurons of the dorsal horn follow a pathway through the anterolateral quadrant of the spinal cord. However, anterolateral cordotomy reveals that all fibers do not uniformly obey this rule. Indeed, this surgical intervention does not involve analgesia. Instead, it causes hypoalgesia, or a reduction in pain in response to a normally painful stimulus. In addition, in a few months, individuals who have undergone this intervention will partially recover their sensitivity [26]. Since regeneration is rather improbable in the CNS, the partial recovery of sensitivity suggests the contribution of more than one pathway. Other pathways are thus available to the nociceptive message, including the lateral spinothalamic tract, the dorsal column-medial lemniscus pathway, and the spinoreticulothalamic tract.

Two of these tracts are responsible for nociceptive afferents: the lateral spinothalamic tract and the spinoreticular tract (or medial spinothalamic tract). A third pathway, the dorsal column-medial lemniscus pathway, is mainly responsible for transporting non-nociceptive information originating from the Aβ fibers. The fibers of the dorsal column-medial lemniscus pathway are divided into gracile tracts (coming from the lower limbs) and cuneate tracts (coming from the upper limbs). These cells do not respond differently to nociceptive and non-nociceptive stimuli, and they project their afferent impulses into the ventrobasal complex [ventral posterolateral (VPL) and ventral posteromedial (VPM)] of the thalamus. They receive information about mild mechanical stimulations and joint movements. Nevertheless, anatomical and clinical studies have shown that the medial region of the dorsal column of the spinal cord play an important role in transporting visceral afferents, including nociceptive afferents coming from the viscera [93].

The lateral spinothalamic tract is, as its name indicates, in a lateral position, and it projects directly toward the lateral thalamic nuclei of the ventrobasal complex. The projections in the ventrobasal complex are also called the neospinothalamic tract. They generally have the characteristics of either specific or multireceptive nociceptors. The projection cells of the spinothalamic tract, mainly coming from laminae I and IV–VI [94], are projected toward the nuclei of the contralateral ventrobasal complex. Their receptive fields are generally contralateral and circumscribed. The fibers of the spinothalamic tract have rapid afferents with relatively precise receptive fields that project toward thalamic and then cortical regions with precise somatotopic representations. The spinothalamic tract, therefore, has the necessary qualities for localization and perception of the sensory-discriminative component of pain [92].

The spinoreticular tract is in a more medial position. Its projections in the medial complex of the thalamus are also called the paleospinothalamic tract. The majority of its afferents come from the deep laminae VII and VIII and are projected toward the medial nuclei of the thalamus and certain structures of the brainstem, including the PAG and NRM [92]. Unlike the spinothalamic tract, the spinoreticular tract has very large receptive fields that sometimes cover the whole body. The spinoreticular tract afferents mostly come from slow C fibers. Those projections lead toward the regions of the brainstem, thalamus, and cortex, which play major roles in memory and emotions. These qualities make it an ideal candidate for having a dominant role in the perception of the unpleasant or motivational–affective aspect of pain [92]. It is by the activation of the spinoreticular tract that we recruit descending analgesia (Diffuse noxious inhibitory control—DNIC) [19].

3.4.1 Visceral Pain: A Specific Pathway

The visceral system is a very sophisticated sensory system implicating the concomitant activity of two extrinsic innervations, vagal and spinal, as well as numerous intrinsic neurons [45]. For example, the intestine has a neuronal system that operates independently but also in relation with the rest of the CNS, known as the brain–gut axis. Several visceral pain syndromes, as the irritable bowel syndrome, present no clear lesion or dysregulation of the painful organ. The brain–gut axis seems to play an important role in these syndromes and may help to better understand the interaction between external events such as a stressful situation and an effect on the symptoms [42]. Emerging data are also stressing the importance of the microbiome, proposing the significance of a «microbiome-brain-gut axis» in some pathological conditions, including pain [4]. These results suggest that alteration in the gut microbial composition is associated with marked changes in behaviors such as mood, pain, and cognition, that are related to a bidirectional communication between the brain and the gut microbiota [79]. Understanding these interactions may lead to treatments acting on the microbiota that will affect brain functions.

3.4.2 Brain, Gut, and Emotions

As for somatic pain, chronic visceral pain is related to both peripheral and central

sensitization. Excitatory and inhibitory descending pathways are also implicated in the visceral system, suggesting an important central influence of visceral sensitivity. Finally, the autonomic nervous system influence on visceral sensitivity may help explain the role of emotions on the modulation of visceral pain. Based on these observations, some chronic visceral pain presents the characteristics of neuropathic pain [45].

Interestingly, we all have experienced what we call a «gut-feeling». For example, a situation that feels uncomfortable without being able to clearly identify why.

William James, at the end of the nineteenth century [39], already proposed that body responses are fundamental to perceive emotions. More recent researches are supporting the importance of our body interoception informing us about states such as well-being or stress that is encoded in the insula and is playing an important role in general emotional states, including our analysis of a pain state [13, 17]. This close interaction between visceral afferences and the insular cortex (IC) may help understand why visceral pain has such important emotional effects.

3.5 Higher Center and Pain

We have known for a long time that pain is a complex sensory and emotional experience demanding the participation of the higher centers of the CNS. Nevertheless, the role of the cortex in pain perception has been demonstrated only recently, despite studies dating back to the beginning of the twentieth century from Head and Holmes proposing that it is only once the nociceptive information is sent to the cortex that we can really speak of pain, since pain is a perception [35, 36]. Because an animal cannot tell us its perception of pain, we must refer to its nociceptive behaviors, suspecting that these behaviors are generally responses to pain. The last few decades have been crucial in identifying the role of the different cortical regions in pain. Dividing the thalamic nuclei into groups that receive afferents from the sensory–discriminative tract and those that receive afferents from the motivational–affective tract can simplify the presentation of the cerebral structures implicated in pain perception.

3.5.1 Imaging Pain Response in Higher Centers

Imaging studies of pain are reporting activation in multiple brain regions including SI, SII, ACC/MCC, insula, PFC, cerebellum, and supplementary motor area (SMA) [18, 29]. In brain imaging, we study the experience of pain by trying to figure out the role of different structures by establishing a link between pain characteristics and the activation of some structures. The «pain matrix» proposed by Melzack [55] paved the way for the imaging studies that found different structures that are implicated in different components of the pain experience. Most of imaging studies are reporting activities in a number of brain sites including sensory (SI, SII), affective (ACC/MCC, insula, PFC), cognitive (ACC/MCC, PFC, SII), and motor (SMA, cerebellum) aspects of pain [18, 29]. However, it has been proposed that there is no specific pain matrix since activities in these regions can also be recorded by different stimulation modalities that are not painful and could then be more related to the salience of the stimuli rather than specific to pain [37].

3.5.2 Pain Matrices

Garcia-Larrea and Peyron [29] proposed that there are at least three pain matrices that are responsible for our complex pain experiences: (1) the nociceptive cortical matrix, (2) the perceptual matrix, and (3) the pain memory matrix.

(1) The nociceptive cortical matrix is projecting from the posterior thalamus nuclei to the posterior insula, medial parietal operculum, and mid-cingulate cortex. This first-order matrix is the earliest response to noxious stimuli.
(2) The perceptual matrix is composed of several cortical regions including the mid and anterior insula, anterior cingulate, PFC, and the posterior parietal area. This perceptual matrix

is different from the nociceptive matrix by the fact that it does not receive direct nociceptive inputs and it can be activated in context not involving pain. It is a context dependent matrix.

(3) The pain memory matrix is composed of several high-orders cortical structures such as the perigenual cingulate, the orbitofrontal cortex, the temporal lobe, and the anterolateral PFC. We know that important changes in pain perception can occur without any nociceptive stimuli and without changing the activities in the pain pathways from the thalamus to the somatosensory cortex for instance. A good example is the empathetic observation of someone in a painful situation that will make us grimacing and feeling as if we were experiencing their pain [38]. We recently found that we can even trigger our endogenous pain inhibitory mechanisms just by observing ourselves or someone else during experimental pain (cold pressor test) [31]. Manipulating the unpleasantness of a painful stimulus by giving it a different meaning, being the less intense or «more pleasant» versus being the most intense or «more unpleasant» in a series of stimuli will totally change our perceived intensity by changing the activity in higher order structures of this matrix [52].

3.6 Specificity of Brain Regions in Pain

Pain is a complex phenomenon constructed around several sensory, affective, and cognitive concepts that are interacting and adapting to our environment in relation with previous experiences. It is then artificial to present different brain structures as being responsible for a specific pain component since each of these structures is influencing how the other structures of the «pain matrix» will code the message. New imaging approaches that are not time-locked to painful stimuli, but rather are measuring more natural ongoing pain in patients using resting state imaging, are demonstrating how dynamic several brain regions are activated during this resting state [46, 88].

For the sake of understanding the neurophysiology and the pathophysiology of pain, it is still interesting to try to understand the neuroanatomical organization of the higher structures that are playing different roles in the experience of pain, keeping in mind that it is not a static but rather dynamic system.

Since the first studies of cerebral imagery of the regions that play a role in pain using positron emission tomography (PET) [77], several subsequent studies have confirmed the participation of the four principal cerebral centers (Fig. 4): the primary somatosensory cortex (SI), in the postcentral gyrus of the parietal lobe; the secondary somatosensory cortex (SII), in the parietal operculum; the anterior and medial cingulate cortex (ACC/MCC), in the cingulate gyrus; and the insula, in the lobe of the IC, which is found under the temporal and frontal lobes, in the Sylvian fissure [12]. Methods that involve making a lesion specific to structures or recording nerve cells in these same localized regions have only allowed us to have a fragmented view of the role of the cortex in pain. We have sufficient data to conclude that cortical structures such as SI contribute to the sensory–discriminative component of pain, whereas the frontal, cingulate, and insular cortical structures are involved in the motivational–affective component [12, 43, 77].

3.6.1 Sensory Discrimination: Primary Somatosensory Cortex (SI)

The spinothalamic tract, originating from the ventrobasal complex of the thalamus, projects toward the primary (SI) and secondary (SII) somatosensory cortices [92]. Injuries to these structures produce a loss of capacity to specify the location and intensity of nociceptive stimulation [9, 43], which confirms their role in the sensory–discriminative component of pain. However, it is important to note that injuries to the somatosensory cortex can sometimes produce the completely opposite effect, hyperalgesia [43]. This phenomenon can be explained by the destruction of the excitatory or inhibitory cortical

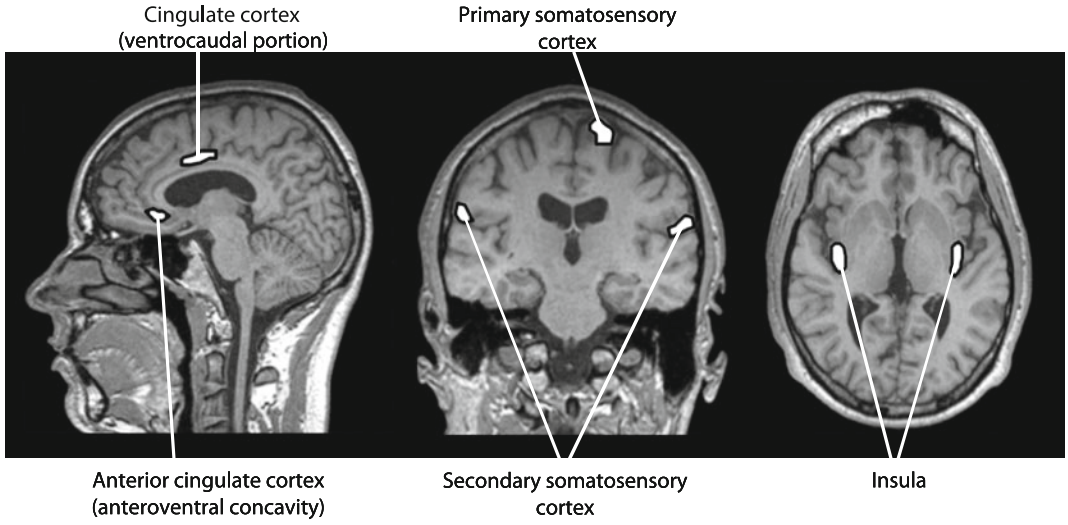

Fig. 4 Some of the cortical structures involved in pain: Schematic representations of the four main cortical structures involved in pain. These regions are the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), the insula, and the anterior cingulate cortex

regions, depending on the extent of the injury to the parietal cortex. Several studies have confirmed the role of the SI cortex in the sensory–discriminative component of pain because of its specific activity in certain cerebral imaging protocols aimed at isolating the nociceptive component of a stimulus [7].

3.6.2 Sensory Discrimination: Secondary Somatosensory Cortex (SII)

Although it appears to be less specifically involved than the SI cortex, the SII cortex also seems to play an important role in the sensory–discriminative component of the location and appreciation of the characteristics of nociceptive stimulation, despite receptive fields of variable and generally bilateral dimensions. In patients who have undergone a hemispherectomy because of chronic untreatable epilepsy attacks, the stimulation of the leg contralateral to the lesion causes the activation of the SI cortex on the same side as the stimulated leg, as opposed to the contralateral activation seen in healthy subjects [63]. This cortical reorganization brings to light the possible participation of networks between SI and SII in enabling a certain plasticity of the somatosensory cortex [44].

3.6.3 The Motivational–Affective Component of Pain

The ACC, MCC, and the insula are regions of the limbic system that play a dominant role in the motivational–affective component of pain. In addition, their wide receptive fields are covering large surfaces of the body, suggesting that these structures participate in general and interoceptive sensations [13, 16].

3.6.4 Motivational–Affective: Anterior Cingulate Cortex (ACC)

Several studies have highlighted the participation of the cingulate gyrus following painful stimulation [85, 101]. Clinical studies in patients who have had injuries to the ACC have revealed a reduction of both clinical [65] and experimental

pain [77]. This region of the limbic system receives its afferents from the medial pathway and plays a dominant role in the motivational–affective component of pain. Visceral pain with a strong affective component, such as that associated with irritable bowel syndrome, preferentially activates this cerebral structure [10], highlighting its role in the affective component of pain. The ACC is highly related to the psychological construct we have about pain. The anticipation of pain is activating the ACC [90].

3.6.5 Motivational–Affective: Insular Cortex (IC)

The complex of the IC has several means of contact with the cortical structures that are classically associated with pain: SI, SII, and cingulate cortices. The insula has several contacts with the limbic structures such as the amygdala and perirhinal cortices, suggesting an important role in the affective component of pain. In some individuals, stimulation of the insular complex produces emotional sensations of fear, and injury to this same structure produces an absence of emotional responses to nociceptive stimulation [82]. The presence of thermoreceptive and nociceptive neurons in the IC has been clearly documented [16]. In one study on Thunberg's thermal grill illusion, which consists of a paradoxical perception of pain in contact with warm and cold juxtaposed bars that would only produce painless hot or cold sensations if they were touched individually, Craig and Bushnell [15] showed that the pain comes from a decrease in tonic inhibition of nociceptive neurons by the simultaneous presentation of hot and cold temperatures. This phenomenon is mainly produced in the insula and might occur with certain pains of central origin [15], which would explain the pain similar to a burn felt by patients with a thalamic syndrome. As we saw earlier, the insula is also the hub for homeostatic signal [14].

3.6.6 Cognitive Control: Prefrontal Cortex (PFC)

The PFC is directly connected to the limbic system and has been demonstrated to be responsible for regulating our emotions, including the motivational–affective aspect of pain [89]. Moreover, the PFC is in direct communication with descending pain modulation pathways, including the PAG. Roy and colleagues [70] demonstrated that this interconnection between the PFC and the PAG is playing a major role in learning and predicting errors, a circuit to learn how to avoid painful situations.

A study of Leknes and colleagues on the reappraisal of painful stimuli is a very nice demonstration of the importance of the PFC on pain [52]. In their study the same stimulus intensity was perceived as unpleasant or pleasant depending on the context where this stimulus was the worst or the least painful. In the worst painful situation, the nociceptive stimuli were presented alternatively with non-painful stimuli. In the least painful context, the same stimuli were presented alternatively with more intense stimuli. In the least painful condition, the subject's perception flipped from a negative to positive hedonics relative to the context. A complex circuitry triggered by the orbitofrontal and ventrobasal PFC was reducing the insula and ACC activity, but also activated the PAG pain modulation pathway.

3.7 Pain, a Multifaceted Perception Needing a Large Brain Network

In summary, our growing understanding of the role of the higher centers in pain allows us to realize the complex balance between the sensory and affective components. It is now easier than ever to accept the importance of the mutual influence between emotions and sensations in the pain experience. Certain higher centers (SI, SII) specialize in the sensory–discriminative component of pain to give precise information on the location, intensity, and all the other characteristics of the nociceptive stimulation. Other centers (ACC, IC) specialize in the emotional appreciation of pain. The affective component is not only associated with the intensity of the stimulation, but it also refers to other emotions, such as

anticipation or fear [68]. For example, we may experience suffering when we attend to the pain of another person, especially when this person is dear to us. A study revealed that empathy for other people's suffering activates the same brain centers associated with the motivational–affective component of pain as if it were our own pain, but without the activity of the centers associated with the sensory–discriminative component [73]. Our perception of the pain of others is, therefore, quite real, in cerebral terms!

3.7.1 Resting State Activity: The Default Mode Network (DMN)

Brain imaging using PET or fMIR was based on a repetitive task, in our case a painful stimulus, subtracted from a control task where the subject was doing nothing. However, we know that doing nothing is not possible. Most of the time the subject will think either at the previous or coming task, or at some other things. A relatively recent tendency is to record what is happening during the baseline, or the resting state [33]. It was no surprise to realize that the brain is not at idle, but very active. The active regions included the medial PFC, medial temporal lobe, posterior cingulate cortex, and lateral parietal cortex [27]. Studies are supporting that this activity is related to connections between these structures for a co-activity or deactivation that may subserve salience, executive control, cognitive, and emotional functions [18].

Studies have shown that the DMN is abnormal in chronic pain patients. Abnormal DMN activity may help understand the focus on pain in chronic pain [1]. The default mode is associated with a "mind-wondering" that is contrasting to living the moment as proposed by the philosophy of contemplative meditation. Interestingly, the main nodes of the default mode network, medial prefrontal and posterior cingulate cortices, were relatively deactivated in experienced meditators [5]. Even relatively new meditators practicing mindfulness get the beneficial effects that are related to changes in the DFN including increased activation in the right dorsolateral PFC and in the left caudate/anterior insula and decreased activation in the rostral PFC and right parietal cortex [80].

A thorough understanding of the neuronal networks of the higher centers allows us to better grasp the nature of the physiology of pain and pathophysiology of certain types of chronic pain conditions. Based on these results, it is obvious that affective and cognitive components are playing major roles in several pain conditions, stressing the need to select an intervention that takes these aspects into account in the treatment of pain.

3.7.2 Interaction of Excitatory and Inhibitory Mechanisms

As we just described, excitatory mechanisms, such as central sensitization , can increase the nociceptive signal while inhibitory mechanisms will decrease the signal. Persistent pain can result from the recruitment of excitatory mechanisms such as central sensitization or the reduction of the efficacy of inhibitory mechanisms [54, 98]. Central sensitization is expressed as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate hyperalgesia, aftersensations, and enhanced temporal summation. Quantitative sensory testing is generally used to characterize these abnormal sensations. On the other hand, efficacy of inhibitory mechanisms is tested using the response of conditioned pain modulation (CPM; also known as diffuse noxious inhibitory control—DNIC).

The recruitment of receptors implicated in the membrane depolarization (e.g., *N*-methyl-D-Aspartate—NMDA) will produce a neuronal hyperexcitability and the resulting pain will be related to endogenous pain excitatory mechanisms [23, 97]. On the other hand, a deficit of inhibitory mechanisms will be related to a reduced activity of descending serotonergic and noradrenergic pathways [58]. Even if two patients present apparently similar pain conditions, the implicated mechanisms may be different and will not respond to the same treatments. For instance, in the case of excitatory hyperactivity (central sensitization), anticonvulsant may be a good treatment choice. However, if a deficit of inhibitory mechanisms is implicated, better

results may be obtained with antidepressant to trigger back serotonergic and noradrenergic endogenous inhibitory mechanisms (DNIC) [99].

Recent studies have highlighted the fact that relatively simple quantitative sensory testing is able to identify a deficit of excitatory (sensitization by temporal summation) versus a deficit of CPM that respond differently to different classes of drugs. For example, studies have shown that a deficit of CPM is a good predictor of the response to duloxetine, a noradrenergic, and serotonergic drug [99], while temporal summation was a good predictor of the response to pregabalin (blocker of neuronal hyperactivity in the class of anticonvulsant drugs) [61, 64]. Interestingly, the response is specific to the mechanisms; CPM efficacy was not a good predictor of pregabalin efficacy while temporal summation was not predicting the efficacy of duloxetine.

These results support that finding new approaches to detect the implicated mechanisms in chronic pain will help guiding the treatment. The different brain imaging techniques are part of the tools that will help identifying specific mechanisms and the specific effects of some treatments [18, 81].

3.8 Chronic Pain: A Central Sensitization Paradigm

Brain imaging studies are used to understand pain mechanisms in healthy subjects, but also to better characterize the mechanisms implicated in different chronic pain conditions. Central sensitization, which we can define as a pain that is maintained by the central nervous system, is probably one of the most accepted theories to understand how pain could persist for so long in patients that present no apparent injury. Understanding the mechanisms of central sensitization is important to help predict and reduce the occurrence of chronification, but also to offer treatments that are adapted to specific pathologies.

Memory and pain share common grounds. For instance, long-term potentiation (LTP), a lasting increase in synaptic strength that is necessary for learning and memory [3], is probably responsible for persisting lower pain threshold or spontaneous pain. It is comparable to central sensitization that is also a synaptic facilitation that is leading to reduced pain threshold and amplification of pain responses [41]. Interestingly, LTP can be induced in the pain pathways by high-frequency stimuli on Aδ or C fibers, but can also be activated by natural noxious stimuli, but only if descending, presumably inhibitory pathways are interrupted or weakened, suggesting an interaction between excitatory and inhibitory mechanisms [71].

4 Conclusion

Pain is a complex phenomenon. The neurophysiology of pain juxtaposes several different parameters. From the periphery to the higher centers, the nociceptive information goes through several steps: sensory conduction, transmission, modulation, and perception. It is then translated into pain behaviors that express suffering and help seeking.

To explain the course of the nerve impulse, we often use simplifications that follow a linear path. However, pain perception is much more than the mere expression of the nociceptive signal. The activity of modulation systems at all levels of the nervous system illustrates the difficulty in establishing a link between the activation of a nociceptor and the pain felt. The sensory aspect of pain is of importance, but the affective component is responsible for most of the pain modulation mechanisms.

Neurophysiological understanding of this modulation process allows us to put it to use for the treatment of pain. It helps maximize the efficacy of drug therapies and opens up a variety of nonpharmacological interventions for patients.

Brain imaging has revolutionized how we can study pain neurophysiology. We realize that pain pathways that were described using lesion methodologies or electrophysiology are confirmed and better understood. We also found new pathways or new regions that are linked to

different behavioral processes linked to pain perception. Several regions of the higher centers playing different roles in the sensory–discriminative, motivational–affective, cognitive, homeostatic, and in the salience of the experience are interconnected and will constantly change our perception of pain. Better understanding this complexity is the only way to better understand the variability of pain responses between patients that seems to have comparable disease. They will also help understand that even if two patients present apparently similar pain conditions, they may not respond to the same treatments depending on the implicated mechanisms.

Brain imaging is not a fishing expedition. In most of the case, we are targeting specific regions in our analysis. However, in some conditions, brain activities could be recorded without being linked to a specific condition in order to understand what is happening during a more natural resting state condition.

The future is really bright for brain imaging. New techniques are emerging very rapidly and techniques such as MRI, PET, and electrophysiology are used in parallel to take advantage of their unique qualities.

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