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Review

Asymmetric Lateralization during Pain Processing

Carolina Roza [1,*] and Anabel Martinez-Padilla [2]

[1] Departamento de Biología de Sistemas, Facultad de Medicina, Universidad de Alcalá, Alcalá de Henares, 28871 Madrid, Spain
[2] Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias e Instituto de Investigación Biomédica de Málaga (IBIMA), Universidad de Málaga, 29071 Málaga, Spain; anabelmp@uma.es
* Correspondence: carolina.roza@uah.es

Abstract: Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". This complex perception arises from the coordinated activity of several brain areas processing either sensory–discriminative or affective–motivational components. Functional studies performed in healthy volunteers revealed that affective–emotional components of pain are processed bilaterally but present a clear lateralization towards the right hemisphere, regardless of the site of stimulation. Studies at the cellular level performed in experimental animal models of pain have shown that neuronal activity in the right amygdala is clearly pronociceptive, whilst activation of neurons in the left amygdala might even exert antinociceptive effects. A shift in lateralization becomes evident during the development of chronic pain; thus, in patients with neuropathic pain symptoms, there is increased activity in ipsilateral brain areas related with pain. These observations extend the asymmetrical left–right lateralization within the nervous system and provide a new hypothesis for the pathophysiology of chronic forms of pain. In this article, we will review experimental data from preclinical and human studies on functional lateralization in the brain during pain processing, which will help to explain the affective disorders associated with persistent, chronic pain.

Keywords: nociception; pain pathways; emotions; chronic pain; opioids; amygdala

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1. Pain Principles

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. According to this definition and in clear contrast with other sensory and somatosensory modalities with a primarily informative role, pain has, in addition, a protective component. Physiological pain acts as an early-warning protective system, alerting about threats and eliciting orientation towards the potentially harmful stimuli. Upon detection, nociceptive signals are rapidly evaluated to generate an adequate response (withdrawal reflex or escape) and to activate circuits involved in learning and memory; both responses are directed to avoid present and future tissue injury, which are essential for the well-being and survival of the organisms. Notwithstanding, individuals that are congenitally insensitive to pain suffer from repeated injuries and cannot heal normally [2]. On the other hand, when pain persists or recurs even when the cause (injury or illness) has gone away it becomes chronic, and since 2018 has been included as a disease in its own right in the International Classification of Diseases (ICD-11, (https://icd.who.int/browse11/l-m/en (accessed on 2 November 2021)) [3]. Chronic pain affects ~20% of Europeans (~95 million people), and the lack of adequate treatments leads to a decreased quality of life, reduced productivity, the appearance of psychiatric symptoms and illness, and increased risk of suicide (see [4] for a review), proving that the emotional processing is a key component of the pain experience.

The fact that persistent pain is commonly associated with depression and anxiety disorder, while fear and stress typically inhibit pain, is a fascinating dichotomy that stresses

the fundamental and complex relationship between emotional and sensory aspects in pain perception. Although lateralization during pain processing has not been extensively studied, the field of affective neuroscience has debated for decades how the brain processes emotions, and two major theories of cerebral lateralization have been proposed. The "right hemisphere hypothesis" suggests that emotions are predominantly processed in the right hemisphere regardless of their affective valence (positive vs. negative [5]). This hypothesis explains why the left side of the face is more expressive when transmitting emotions, the emotional intonation (prosody) of auditory stimuli is acknowledge better when presented to the left ear, and visual stimuli presented to the left visual field elicit greater autonomic and emotional-induced responses. The "valence-specific hypothesis" based on the emotional perception claim that the right hemisphere would be responsible for the processing of negative emotions (and pain); therefore, positive emotions would be predominantly processed by the left hemisphere [6]. Recent findings suggest that both hypotheses are valid and responsible for specific components of the emotion (such as generation, perception, and regulation) [7,8]. Both scenarios posit that functional lateralization also occurs during pain perception, involving a differential recruitment of specific brain areas located in the right or left hemisphere, together with an asymmetrical distribution of neurotransmitter signaling pathways involved in pain.

Neural Pathways and Brain Areas Involved in Pain Processing

Pain experience is the end product of a complex series of circuits that involves sequential processing by different neuronal networks in areas and pathways coordinated in time and space, and in contradiction to other sensory modalities, there is no single pain center [9,10] (see Figure 1).

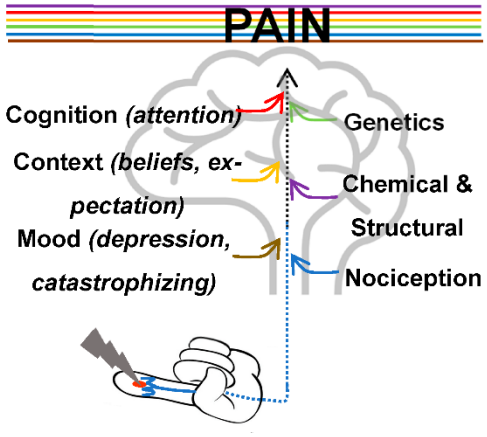

Figure 1. Pain is the end product of a complex neuronal process. The scheme shows the many factors that influence the nociceptive signals initiated at the peripheral skin when nociceptive primary afferents (our "*pain sensors*") are activated by potentially harmful stimuli.

The primary afferent nociceptor is the first component of the nociceptive system, capable of detecting potentially harmful stimuli presented at the periphery by means of specialized receptors [11]. Nociceptors are pseudo unipolar neurons that have their soma in the trigeminal ganglia (TG) or dorsal root ganglia (DRG) (related with sensory information arising from the head and trunk and limbs, respectively). The peripheral branch is found in the skin, viscera, joints, and muscles, whilst the central projection terminates ipsilaterally from the spinal trigeminal nucleus or dorsal horn of the spinal cord (see Figure 2C). Nociceptive inputs are processed by local spinal circuits and subsequently secondary projecting neurons will carry nociceptive signals to areas within the telencephalon by means of two main disynaptic routes: the spino-thalamico-cortical (STT) and the spino-parabrachial-amygdala (PB) pathways (depicted in Figure 2). These precise targets have been assessed in non-human primates following the pathways marked by stained herpes viruses, which upon injection at the dorsal horn of the spinal cord are transported rostrally

to infect thalamic projection neurons, and from there onto different cortical areas by means of transsynaptic transport [12].

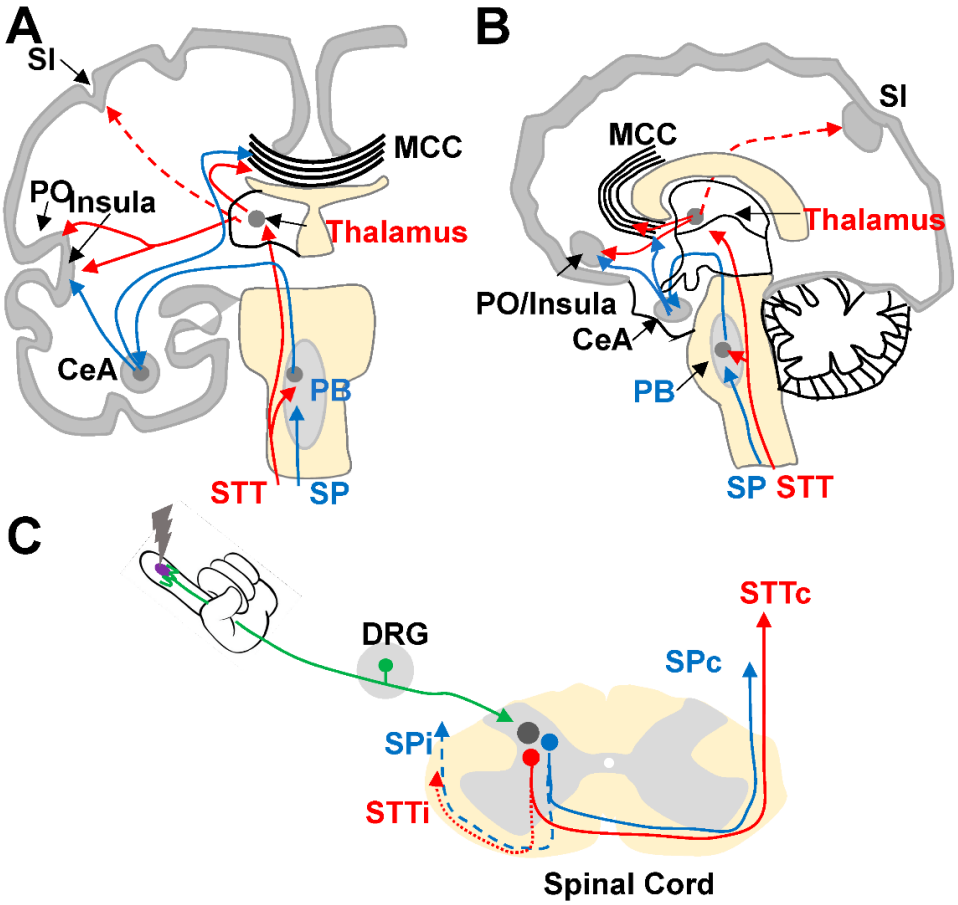

Figure 2. Supraspinal nuclei involved in pain processing located on the coronal (**A**) and sagittal (**B**) planes and ascending pathways from neurons located in the spinal cord that receive inputs from the peripheral nociceptors (**C**). Primary afferent nociceptors (in green) with specialized terminals in the skin and cell bodies in the DRG (dorsal root ganglion) send signals to the spinal cord. Second-order neurons in the dorsal horn of the spinal cord send the processed information to the thalamus via the spinothalamic track (STT) to reach cortical areas responsible for sensory–discriminative and sensory–motor aspects of pain (red lines), including the posterior insula and PO (parietal operculum) cortices, MCC (midcingulate cortex), and SI (primary somatosensory cortex). On the other hand, the spinoparabrachial tract (SP) ends at the parabrachial nucleus (PB) of the Pons from where the information reaches limbic areas responsible for the affective and emotional aspects of pain (blue lines), including the CeA (central amygdala–anterior insula), aMCC (anterior midcingulate cortex), and iMCC.

This study revealed that in non-human primates, most axons from the projecting neurons in the spinothalamic tract (STT) cross the midline at their corresponding dermatome in the spinal cord, ascend in the anterolateral tracts located in the white matter, and terminate in different nuclei of the thalamus, from where they target the posterior insular cortex (~40%), medial parietal operculum (~30%), and motor sections of the midcingulate cortex (~24%). Interestingly, only ~5% of the thalamic projections reached the primary somatosensory cortex [12]. Earlier functional studies in human volunteers described that during pain experience, corresponding brain areas that are likely responsible for the discriminative aspects of the nociceptive signals (localization, timing, or intensity, among others) are activated. These areas and pathways were entitled as the lateral pain system [13], although other authors refer to them as a "first-order" or "sensory-specific" network [14], reformulating the concept of the pain matrix [15].

Tracing studies in animals [12] and intracranial electroencephalography in humans revealed that projecting neurons in the spino-parabrachial pathway reach the limbic system via the amygdala complex [15,16]. Most of the spinal projections are contralateral (60%), while the remaining (40%) travel ipsilaterally or even bilaterally [17]. This pathway is related with the affective and motivational components inherent to pain perception [18] and constitutes the "second-order" network, which includes sections of the anterior insula (AI), anterior mid-cingulate (aMCC), lateral prefrontal, and posterior parietal areas. This "emotional network", which can be activated by stimuli other than pain, is assumed to be crucial for the "salience" attributes of noxious stimuli. Combined activity from "first-" and "second-order" networks is sufficient to elicit a conscious perception of pain [15,16,19]; however, the final experience still depends on ongoing internal states of the individual (such as beliefs, emotions, and expectations), which result from the activation of a "third-order" or cognitive neural network that includes processing from circuits located at the anterolateral and orbitofrontal areas and ventral tegmental and perigenual or limbic networks [14].

Nociceptive information sensed by peripheral nociceptors located in the left side of the body is mostly processed in the right hemisphere of the brain, and vice versa. However, according to the scientific literature (see above), the innervation of many brain areas is bilateral, providing an anatomical substrate for two-sided processing that would allow for functional lateralization. From the mid 19th century, neuroscientists and psychologists have been exploring the anatomical specialization within the brain in order to understand how lateralization can influence diverse behaviors and functions. Thanks to the application of modern techniques in neuroscience research, such as electrophysiology and functional imaging, it has been possible to gain insight into functional lateralization of pain, although most interestingly we will explain below that recent evidence illustrates that this phenomenon might contribute to the transition from acute to chronic pain [14,20].

2. Experimental Basis for Functional Lateralization during Pain Processing

Neuroimaging techniques provide non-invasive ways to study the activation of brain areas in awake humans performing different tasks. Despite the limitations, brain imaging has helped to identify areas activated during pain experiences (reviewed [21]) and how such experiences are highly influenced by many factors, such as the context, level of attention, mood, or genetical factors, among others [22]. It is important to stress that there is no such thing as a specific brain signature for pain, meaning activity in these areas is non-specific for pain and that pain cannot be inferred by observing activity in pain networks [23].

During pain stimulation, brain imaging studies in healthy humans show bilateral activation of brain areas included in the first- and second-order networks, such as the mid-posterior insula, anterior insula, and posterior cingulate [10,21,22,24–28]. Patients with a severed corpus-callosum are able to detect nociceptive stimuli applied unilaterally [28,29]; moreover, they also showed bilateral activation of pain-related brain areas, regardless of the stimulated side [30,31], supporting the idea that the activation of both hemispheres does not depend exclusively on cortical connections, and most likely relies on direct peripheral inputs (Figure 2 depicts the anatomical substrate for ipsilateral connectivity).

In addition, some of the functional studies in healthy volunteers described a preferential activation of brain areas located in the right hemisphere, including the anterior cingulate cortex (ACC) [25], although other authors suggested that right lateralization is not specific for pain detection as it is with attention, as it also occurred with innocuous stimulation [28]. Therefore, when the subject's attention is focused towards a noxious stimuli, certain cortical areas (prefrontal and posterior parietal) are specifically activated only in the right hemisphere [32]. However, latter experiments reach opposite conclusions and were unable to detect preferential right lateralization [27]. Whether these particular areas are involved in pain perception or work as an all-purpose alerting system is beyond the scope of this review; however, attention and pain are not only related, but it has also been shown that patients with chronic pain present cognitive difficulties due to attentional interference [33]. Moreover, pain catastrophizing (described in terms of excessive focus on

pain, feeling of helplessness, and magnification of ongoing or future pain) interferes with normal body movements and correlates with pain-related disabilities [34].

Data from brain imaging in humans showing asymmetric lateralization are further supported by results from preclinical studies that allow for characterization at the cellular level. Unfortunately, studies in rodents are scarce, and to our knowledge have only covered the amygdala.

2.1. Asymmetric Lateralization during Pain Processing in the Amygdala

The amygdala, firstly described in the 19th century, was named because of the almond shape of one of its many nuclei. This complex structure belongs to the limbic system and has been extensively studied in the context of fear conditioning, although most recently has been shown to have an important role in processing noxious information with an impact on pain experience [35,36]. The resolution of neuroimaging techniques in pain studies is not fine enough to differentiate activation of different amygdala subnuclei [37], which explains why some studies have consistently report that the amygdala is selectively activated in humans by painful stimuli and showed increased activation in chronic pain conditions, while others have reported the opposite—amygdala deactivation [35,36]. Nevertheless, the only study in humans that evaluated functional lateralization during pain processing showed that pain evoked by gastric distensions in healthy volunteers activated bilateral areas from first- and second-order networks (excluding SI), although the activity in the amygdala was significantly lateralized towards the right hemisphere [38], which is supported by data obtained from animal studies.

Anatomically, the amygdala is composed of several nuclei [39], many of which are involved in pain processing and are depicted in Figure 3. Tracing studies in rats demonstrated that the central nucleus of the amygdala (CeA) receives direct nociceptive inputs from the spinal cord via the pontine parabrachial nucleus [40]. Other nuclei receive indirect signals from the brainstem, thalamus, and anterior insula. The outcome of the processing at the amygdala represents an emotional judgement [35].

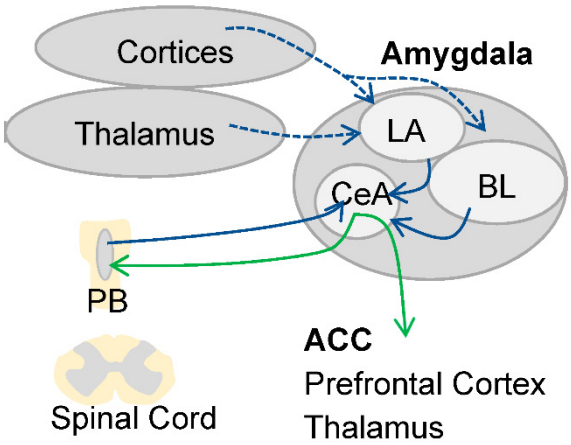

Figure 3. Processing pain at the Amygdala involves several circuits within different subnuclei. CeA, BLA, and LA represent the central, basolateral, and laterocapsular amígdala subnuclei, respectively. The scheme shows the main direct and indirect inputs (blue) and outputs (green). PB—parabrachial nucleus.

Electrophysiological recordings in vivo from experimental animals described the presence of neurons located in the amygdala that responded to noxious stimulation of the peripheral tissues that increased their excitability during chronic inflammation (reviewed in [35]). However, most interestingly, a series of experimental evidence at the cellular level further demonstrated a clear asymmetrical lateralization between the left and right central subnuclei and amygdala during pain processing. For example, in mice, subcutaneous injection of the pro-inflammatory agent formalin in the plantar surface of the hind paw produces licking, lifting, and flinching of the injected paw (indicative of pain) and increases

the thermal sensitivity of both paws (indicative hyperalgesia). In addition, it also induces phosphorylation of extracellular-signal-regulated kinases 1 and 2 (or ERK1/2, indicative of neuronal activation) in the right amygdala, regardless of the injected paw [41]. Furthermore, pharmacological blockade of ERK or the mGlu5/ERK pathway in the right CeA (but not the left CeA) decreased the pain behaviors and hypersensitivity induced by the formalin injection, independently of the inflamed side [42,43].

Similarly, in naïve rats, neurons recorded in the right and left amygdala showed similar background discharges and evoked responses. However, when monoarthritis was induced in the right or left knee, the expected signs of sensitization (increased discharges at rest and upon knee stimulation) were only observed in the right amygdala [44]. Unilateral noxious stimulation in rats increased c-fos expression (a marker indicative of neuronal activation) bilaterally in the PB, and also in the CeA, where the number of activated cells was significantly higher in the right CeA, regardless of the side of stimulation [45].

Functional asymmetric lateralization also occurs during processing of visceral pain. In visceral structures, such as in the urinary bladder, which possess bilateral innervation, it was shown that the visceromotor responses (withdrawal reflex that accompanies visceral pain) evoked during noxious distension of the urinary bladder in mice were increased during simultaneous activation of the right CeA. Most interestingly, a similar increase in visceromotor response was seen upon silencing of the left CeA [46,47]. In this line, referred pain and sensitization during cyclophosphamide-induced urinary bladder inflammation was reversed upon inhibition of the left amygdala [47].

Although the underlying mechanisms are still far from clear, this form of lateralization is certainly fascinating (and so far not described for other neurophysiological systems).

2.2. Signs of Asymmetric Lateralization during Pain Processing in Other Brain Areas: Non-Functional Studies in Humans

Most of the studies on pain lateralization have focused on the amygdala; however, seldom reports exists on pain lateralization involving other brain areas, and in general terms the evidence points towards asymmetric lateralization towards the right hemisphere. For example, although rare, thalamic pain might develop following stroke-induced brain damage; it is of note that thalamic syndromes develop more frequently after right-sided lesions [48]. Patients with chronic complex regional pain syndrome, who exhibit exaggerated painful response and abnormal autonomic function, showed signs of gray matter atrophy affecting the anterior insula, prefrontal cortex, and nucleus accumbens from the right brain [49].

2.3. Asymmetric Lateralization of Pain Processing in Patients with Neuropathic Pain

Neuropathic pain is a chronic form of pain that develops after direct damage to the somatosensory nervous system, and it is estimated to affect ~7–10% of the population in Europe, representing an annual cost per patient in terms of medical treatment and lost work of about €10,000 [50]. Neuropathy might be secondary to diabetes and viral infection (i.e., shingles), but most commonly arises from trauma or compression of nerve tissues (i.e., carpal tunnel syndrome, trigeminal neuralgia). It is extremely difficult to treat (even refractory to opioid analgesia) and associated with comorbidities such as sleep disturbances and depression or anxiety. Not surprisingly, in patients with chronic pain, brain imaging revealed a functional shift from somatosensory to limbic brain areas during the transition from acute to chronic pain [14,20]. Despite the differing etiology, neuropathic pain patients share a series of common neurological symptoms, such as allodynia or "touch-evoked pain", defined as pain due to a stimulus that does not normally provoke pain; hyperalgesia or increased pain sensitivity to a stimulus that normally provokes pain; and finally, spontaneous pain or pain in the absence of stimuli.

Allodynia is quite a bizarre anomaly in terms of neurophysiology that continues to puzzle pain researchers, who struggle to explain why the activation of touch receptors is able to evoke pain. Brain imaging studies have consistently shown a differential pattern of activation when stimuli are applied in areas in which allodynia has developed, as

compared to same stimuli applied to normal skin. Stimulation in normal skin produces a bilateral activation of the operculoinsular cortex (OI), with a clear bias towards the contralateral site. However, when stimuli are applied in areas of hyperalgesia or allodynia, activation occurs ipsilaterally to the stimulated site ([9,51–53]). Taking together the results from those studies, it has been proposed that an enhancement of ipsilateral activity might well reflect a disinhibition of the ipsilateral spinothalamic pathway, whereby activity in normal conditions is muted by contralateral pathways. This imbalance would be subsequently interpreted as an increase in the magnitude of the stimuli, explaining the positive symptoms [14]. Surprisingly, none of the studies have yet provided significant differences in brain processing in areas related with emotional processing, which might be due to the lack of resolution and discrete number and variability within patients.

3. Lateralization of Neurotransmitter Systems Involved in Pain Processing

Asymmetric Lateralization of Opioid Receptors in Areas Involved in Pain Processing

The endogenous opioid system (EOS) is a critical neurotransmitter system regulating the presentation and processing of emotions and pain [54]. This system includes three opioid receptor types, μ- (MOR), δ- (DOR), and κ- (KOR), which are preferentially activated by β-endorphin, enkephalins, and dynorphins, respectively. They constitute the pharmacological target for opioid analgesia, which is still proven as the most effective painkilling approach for most forms of severe pain. Activation of the endogenous opioid system is consistently associated with both pleasant and unpleasant emotions. In general, exogenous opioid agonists facilitate approach-oriented emotions (anger, pleasure) and inhibit avoidance-oriented emotions (fear, sadness). Endorphins and enkephalins are positive reinforcers and their interactions with MOR and DOR modulate positive emotional states. On the other hand, activation of KOR produces aversive effects in animals and dysphoria in humans, and concomitantly upregulation of dynorphin may lead to anhedonia and depression (reviewed in [55]).

Lateralization of positive and negative emotions (and pain) [8] might suggest an asymmetric distribution of neurotransmitter systems that matches the opposing effects of the EOS. This idea has been recently supported by a study examining symmetric areas of left and right brain biopsies from deceased subjects. From the examined areas (pgACC—a subregion in the MCC; prefrontal cortex; caudate; putamen) strong lateralization to the left hemisphere was found for LER (Leu-enkephalin-Arg, a MOR and DOR agonist) at the left pgACC and for MEAP (Met-enkephalin-Arg-Phe, a KOR and MOR agonist) at the right pgAA [56]. The pgAAC has anatomical connections with the amygdala, which has high levels of endogenous opioid peptides and receptors [57]; unfortunately, EOS lateralization in the amygdala has not been addressed yet.

The spinal cord is the target for the so called descending modulatory pathways, which inhibit incoming pain information by dampening nociceptor inputs to second-order neurons [58]. Nociceptors and local circuit neurons are known to express opioid receptors, although the main absolute expression for genes coding for the three opioid peptides and their receptors was shown to exhibit a clear differential pattern. In naïve rats, dynorphin and its receptors were significantly elevated in the left dorsal horn (sensory) as compared to the right, and the three receptor genes were significantly elevated in the left ventral horn (motor) as compared to the right [59]. These data reveal that asymmetry of pain processing already occurs in the spinal cord, which is the first relay center in the somatosensory system.

4. Concluding Remarks

Although still very limited, experimental data from clinical and preclinical studies have provided evidence for functional lateralization during pain processing. In humans, asymmetric activity seems to be a consequence of chronic pain, which is present with emotional and cognitive comorbidities. Concomitantly, animal studies showed a preponderance towards activation in the right amygdala in experimental pain models, supporting

the relevance of emotional circuits for pain perception and emphasizing the need for a multidisciplinary approach to manage chronic forms of pain.

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