

Review Article

Neuroplasticity in chronic pain: insights into diagnosis and treatment

Sahar M. Jaffal

Pharmacy Department, College of Pharmacy, Amman Arab University, Amman, Jordan

ABSTRACT

Chronic pain is a universal problem that directly evolves the central nervous system, altering both its structure and function. This review discusses neuroplastic alterations in critical areas in the brain like the anterior cingulate cortex, insula, prefrontal cortex, primary (S1) and secondary (S2) somatosensory cortices, and thalamus. These regions exhibit gray matter decrease and changes in connectivity during chronic pain. Several cortical networks, mainly the central executive network, the default mode network, and the salience network exhibit neuroplasticity which reallocates cognitive and emotional resources to pain processing. Thus, it was reported that sensitivity to pain enhances emotional suffering, indicating that altered connectivity and functional reorganization of these networks support maladaptive pain processing and underpin chronic pain persistence. Neuroplasticity-focused treatments such as brain stimulation, neuro-feedback, and exercise-based therapies constitute potential interventions for preventing such negative changes. Further, innovative neuroimaging biomarkers are effective in demonstrating precise neural changes and in providing information about the diagnosis of chronic pain syndromes. This review highlights neuro-plastic changes in chronically painful patients and acknowledges the brain's plasticity as a target for chronic pain treatment. It, also, points to the diagnostic strategies and practical interventions that address these alterations.

Keywords: Brain; Central Nervous System; Chronic Pain; Default Mode Network; Gyrus Cinguli; Neuronal Plasticity; Prefrontal Cortex; Somatosensory Cortex; Thalamus.

INTRODUCTION

Chronic pain is an interminable and multifaceted health problem that is experienced by many individuals worldwide. In contrast to acute pain, which is usually a warning sign of an issue that needs medical attention, chronic pain continues even after the body has healed from an injury, sometimes with no identifiable cause [1]. Chronic pain for a long duration can alter neuronal plasticity at the structural and functional levels of the central and

peripheral nervous systems (CNS and PNS, respectively) [1]. Neuropathic pain is often caused by a primary lesion of the nervous system such as nerve or spinal cord injury, which leads to maladaptive plasticity and central sensitization of the nociceptive pathways. Also, chronic pain changes the signal and perception of pain and causes hypersensitivity to painful stimuli, known as hyperalgesia and non-pain stimuli such as allodynia [2]. In more detail, chronic pain-related neuronal changes consist of structural plasticity and functional reorganization. Struc-

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Correspondence: Sahar M. Jaffal

Pharmacy Department, College of Pharmacy, Amman Arab University, Jordan Street-Mubis, Amman 11953, Jordan

Tel: +00962787924254, E-mail: s.jaffal@aau.edu.jo



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tural plasticity means **modifications in discrete neuronal structures, including synaptic density, dendrites branching, and gray matter decrease especially in pain-related networks like the anterior cingulate cortex (ACC), insula, and prefrontal cortex (PFC)** [1]. Depending on the type of pain, the changes that are brought about can last for years, even when the pain itself has been addressed [3]. Meanwhile, plastic reorganization occurs at the system level in which specific dynamic connectivity within brain regions impacts how pain is perceived and modulated at the cortical and subcortical levels [4]. Such structural and functional neuronal changes are brought about by neuronal plasticity, the brain's capacity to respond to stimulus by changing synaptic connections. Notably, plasticity is detrimental in chronic pain and helps in developing chronic pain [5]. These changes indicate that they mainly occur in areas responsible for modulating pain such as the somatosensory cortex, hippocampus, anterior insula, and the thalamic region where neuroplasticity changes, pain transmission, and emotions of pain occur [6]. The aim of this review is to highlight the structural and functional modifications that characterize acute and chronic pain at the synaptic and circuit level and to identify the effects of these changes on the CNS with an emphasis on the areas related to pain sensation or perception, its regulation and the consequences of diagnosis and treatment of pain. Analyzing neuronal alterations in chronic pain makes it possible to determine therapeutic interventions that can reverse these maladaptive processes and enhance pain relief approaches.

MAIN BODY

1. Pain pathway

It is well known that pain is a complex pathway that involves the release of different mediators after exposure to noxious stimuli, sending the signals to the CNS, which, in turn, sends endogenous analgesic signals through the descending nervous system. **Fig. 1** depicts multiple regions that are involved in this pathway.

1) Primary (S1) and secondary (S2) somatosensory cortices

The pain matrix encompasses a network of brain regions involved in pain perception and modulation. The S1 and S2 somatosensory cortices play a pivotal role in processing the sensory-discriminative aspects of pain [7]. S1 is

responsible for encoding the location and intensity of painful stimuli, while S2 integrates this information and contributes to the perception of pain intensity and the emotional response to pain [7]. These regions collectively contribute to the sensory and affective dimensions of pain perception [7]. A large body of knowledge showed that S1 and S2 somatosensory cortices are important regions in pain matrix framework. Also, Worthen et al. [8] reported a differential role for the S1 and S2 regions in pain with evidence for the involvement for S1 in affective processing. In more detail, the authors recorded magnetoencephalography in male participants during a visceral pain experiment and highlighted the role of S1 in sensory and attentional aspects of pain processing as well as S2 in encoding the characteristics of the stimulus. Remarkably, a recent study revealed that the peripheral immune response mediated by neuropathic pain is correlated with central amygdala and somatosensory cortex via vagal projections to the spleen [9]. Furthermore, current views point to the fact that enhancing cortical excitatory activity can be a valuable way to control neuropathic pain [10]. In more detail, by using patch clamp recording, it was found that the pharmacological or optogenetic enhancement of cortical activity decreased behavioral hypersensitivity that is induced by injury in a neuropathic pain model of transient spinal cord ischemia [10]. Additionally, it was reported that S1 shows paroxysmal discharges and hyperexcitability after the spinal cord injury [10]. All of the aforementioned studies showed that plasticity in the S1 and S2 regions is implicated in pain conditions and the interventions.

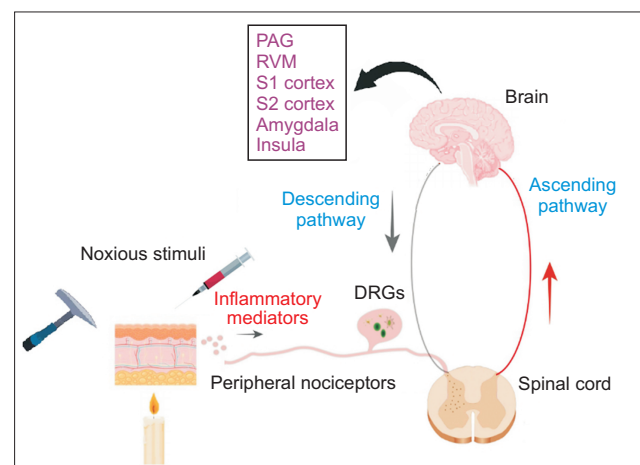


Fig. 1. Pain pathway. PAG: periaqueductal gray, RVM: rostromedial ventromedial medulla, S1: primary, S2: secondary, DRG: dorsal root ganglion.

2) Descending pain modulatory pathways

The descending pain modulatory system is a critical mechanism in endogenous pain control, involving the periaqueductal gray (PAG), the rostroventromedial medulla (RVM), and the spinal cord. Notably, the PAG integrates input from cortical and subcortical regions to modulate nociceptive transmission through the RVM and the dorsal horn of the spinal cord [11,12]. This pathway facilitates both inhibition and facilitation of pain, underscoring its dual role in modulating the experience of pain [12]. Dysregulation within this system has been implicated in chronic pain conditions, highlighting the importance of understanding its mechanisms for developing targeted therapies [12]. Descending pain modulatory systems have been studied and characterized in animal models and by using brain imaging techniques and deep brain stimulation (DBS), and are implicated in the mechanisms of action of analgesic drugs. It is well-known that there is communication between descending pain modulatory circuits, the cortical and subcortical regions that are responsible for the motivational, emotional, and cognitive processes [13]. Accordingly, dysregulation of descending pain modulation is associated with chronic pain. As such, the treatment or the protection from chronic pain states is linked to descending pain modulatory systems such as serotonin/norepinephrine reuptake inhibitors that enhance the activity of the spinal noradrenergic system [13]. In details, growing evidence depicted that PAG activates a powerful analgesic effect and receives inputs from higher brain centers [14]. It is involved in the descending endogenous pain inhibitory system and is a vital area for pain modulation through its interactions between ascending and descending signals [14]. The PAG influences descending pain modulation primarily through its reciprocal connections with the RVM [15]. Also, the midbrain PAG inhibits nociceptive inputs to neurons in the sacral dorsal horn *via* alpha 2 (α_2) adrenergic and μ -opioid receptors [15].

3) Acute pain and neurological pain signature (NPS)

The NPS is a multivariate pattern of brain activity that serves as a neural biomarker for pain perception. It involves the use of machine learning to distinguish pain-related brain activity from non-pain-related activity. The concept of NPS was introduced in a groundbreaking study published in 2013 by Wager et al. [16]. This study utilized machine learning and pattern-recognition algorithms to analyze functional magnetic resonance imaging

(fMRI) data from individuals subjected to controlled painful stimuli. The researchers identified distinct brain regions and activity patterns consistently associated with acute pain, culminating in the formation of the NPS. Importantly, the NPS is crucial for the identification of pain-specific activation in regions such as the insula, ACC, and thalamus, allowing for more precise identification of chronic pain conditions [16]. A plethora of evidence shows that the NPS is characterized by increased activity in several brain regions traditionally associated with pain processing, including the ACC, insula, thalamus, S1, and S2 [16]. Additionally, the NPS is associated with decreased activity in regions such as the ventromedial prefrontal cortex (vmPFC), which may reflect the suppression of competing cognitive or affective states. While the NPS was originally developed for acute pain, its principles can be extended to study chronic pain conditions. Chronic pain involves changes in brain function and connectivity, thus the NPS may help in identifying these alterations [17]. By observing changes in NPS activity, researchers can determine how well a drug reduces pain at the neural level. López-Solà et al. [17] explained how the NPS responds to non-steroidal anti-inflammatory drugs, providing preliminary evidence that fMRI-based measures respond to acute osteoarthritis (OA) pain and are sensitive to naproxen. Taken together, multiple studies underscore the NPS's potential as a reliable and objective biomarker for pain, with applications in clinical diagnosis and personalized pain management strategies.

4) Chronic pain and its effects on the CNS

Several studies revealed that chronic pain affects all aspects of the CNS and profoundly alters both the peripheral and central systems [1]. However, neuroimaging investigations showed structural and functional alterations in given areas connected to pain processing such as the ACC, PFC, and insula [1]. These areas are involved in pain's sensory, emotional, and cognitive aspects and reveal a high level of maladaptive plasticity during chronic pain conditions [1].

2. Neuronal plasticity in chronic pain states

1) Structural and functional plasticity

It is widely accepted that chronic pain causes structural and functional neuronal plasticity, including synaptic plasticity. Synaptic plasticity is crucial to the progression of chronic pain through the brain structures that are in-

involved in pain processing including the ACC and insular cortex. Regarding structural changes, previous studies elucidated that the brain regions that are involved in pain processing such as the ACC and PFC exhibit gray matter atrophy and cortical thinning, correlated with increased pain duration and intensity [18]. These structural alterations affect the typical brain architecture and are related to impairment in pain modulation. In addition, long-term potentiation (LTP), a process related to learning and memory has been recorded in these areas during chronic pain conditions [3]. In greater detail, LTP enhances pain signals and helps in developing chronic pain [3]. In neuropathic pain, it was reported that spinal dorsal horn changes occur where the synaptic activity increases leading to central sensitization, a state of pain hypersensitivity [19]. Additionally, structural changes in neurons are considered a hallmark of chronic pain. Research studies explained that neuronal loss and reduced dendritic spine pruning in the secondary motor cortex in neuropathic pain are correlated to motor disorders and increased pain sensitivity [18]. Moreover, it was reported that the perineuronal net (PNN), a component of the extracellular matrix surrounding the neuron and regulating synaptic plasticity was involved in developing chronic pain [18]. In mice with chronic inflammatory pain, PNNs of somatosensory cortex and PFC increased due to chronic pain [20]. Furthermore, it was revealed that pain disrupts the mechanisms of signaling within the brain and spinal cord as it progresses to chronicity [20]. For example, several lines of evidences revealed that the deregulation of the gamma-aminobutyric acid (GABAergic) system in the nervous system in neuropathic pain led to the inhibition of pain signals leading to persistence of pain [21]. Also, it was shown that there are neuroplastic changes during chronic pain in the brainstem, which is a center of pain regulation [22]. Additionally, the current fMRI findings revealed a spectrum of changes within the PAG and rostral ventromedial medulla, which are parts of the descending pain inhibition network [21]. Regarding functional changes, it was shown that chronic pain results in changes to resting state networks (RSNs) with the default mode network (DMN) networks such as being involved in self-reflecting activities and emotions [18]. In addition, it was found that reduced connection within the DMN has been associated with increased pain sensitivity and perception of pain [4]. Previous reports shed light on the fact that the brain's functional architecture is disturbed by chronic pain, especially RSNs like the central executive network (CEN), salience network (SN) and DMN [23,24].

The three core networks are the CEN, DMN and SN.

The SN plays a pivotal role in the anterior insula that is involved in the regulatory and cognitive, affective functions such as emotional responses, empathic processes, and interoceptive awareness [25]. The ACC and anterior insula, which form part of the SN, segregate the most relevant extrapersonal and internal stimuli to guide behavioral functions [26]. Consistent with this finding, a decrease in the functional connectivity of SN to the right posterior insula was reported in adolescent patients with chronic fatigue syndrome compared to healthy people [25]. Further, pain intensity was correlated with the functional connectivity of the SN to the caudate and left middle insula [25]. Moreover, the right anterior insula plays a causal role in demonstrating competitive interactions during the processing of cognitive information through a switch between the CEN and the DMN [26].

Regarding the CEN, it is crucial for manipulating information in working memory, and for decision-making in the context of goal directed behavior [26]. The CEN encompasses both the lateral posterior parietal cortices and dorsolateral prefrontal cortices (dlPFC). Deficits in this network reflect disturbances in the executive control functions and working memory [25]. Meanwhile, the DMN is anchored in the vmPFC and posterior cingulate cortex (PCC) where alterations in the DMN are associated with deficits in self-referential mental activity [25]. Also, the CEN, anchored by the dlPFC and posterior parietal cortex, is essential for working memory and cognitive control. Meanwhile, the SN network that is centered on the anterior insula and the ACC, detects and prioritizes salient stimuli, including painful ones, facilitating rapid responses to critical events. The DMN, comprising the medial PFC and PCC, is associated with self-referential thought and mind-wandering [27,28]. In fact, chronic pain disrupts the connectivity of the CEN, dlPFC, SN and CEN, leading to impaired cognitive function, emotional dysregulation, and altered pain perception. These disruptions highlight the need for targeted interventions to restore network balance and mitigate chronic pain symptoms [27,28]. Taken together, a remarkable amount of literature has shown that self-referential signal processing, sensory input perception, and affective response modulation depend on these anticipated linkages. These networks' after-connections are reinforced and reorganized in chronic pain, leading to changes that increase pain sensitivity, and diminish cognitive function. Chronic pain and its effect on mental health are exhibited in these changes in connection and network dynamics [23,24].

2) Astrocytes and neuroinflammation in chronic pain plasticity

Astrocytes and microglia describe a class of glial cells that play pivotal roles in establishing chronic pain. Reactive astrogliosis is an aberrant cell response where astrocytes get stimulated, consequent upon injury or chronic pain [29]. In glial cells, pro-inflammatory gliotransmitters and cytokines which modulate nociceptive implication and synaptic plasticity are released [29]. Furthermore, earlier studies described that the cross-talk between neurons and astrocytes initiates pain sensitization and is critical for chronic pain resolution. Thus, its impact on neuropathic pain pathology cannot be ignored [21,29]. Activated glial cells (as markers for neuroinflammation) also contribute to pain by modulating neurons and synapses [21]. In more detail, astrocytes and microglia release pro-inflammatory cytokines such as tumor necrosis factor- α and interleukin- 1β that, collectively, enhance the excitability of pain-processing neurons [21]. These inflammatory processes are associated with alterations in early synaptic and structural plasticity that generate persistent pain.

3) Epigenetic mechanisms in chronic pain plasticity

Previous studies revealed that epigenetic changes including DNA methylation and histone acetylation play essential roles in governing the plasticity implicated in chronic [30]. Thus, histone deacetylases and DNA methyltransferases epigenetic factors control gene expression in response to pain stimuli [30]. To elaborate, it was found that enhanced DNA (cytosine-5-)-methyltransferase (DNMT3a2) protein expression in the spinal cord contributes to maintaining central sensitization and chronic inflammatory pain [30]. Consequently, new treatment strategies for chronic pain can be established to reverse the epigenetic modifications. Previous studies have demonstrated that suppression of the histone deacetylase 4 (HDAC4) function in spinal neurons decreases sensitization to pain and normalizes the expression of connectivity in neural circuits [30].

For instance, increased expression of DNA (cytosine-5)-methyltransferase 3a2 (DNMT3a2) in the spinal cord has been implicated in the persistence of central sensitization and chronic inflammatory pain. DNMT3a2 is known to hypermethylate promoters of genes involved in anti-nociceptive pathways, effectively silencing their expression and promoting pain sensitization [31]. This discovery highlights the potential of targeting DNMT3a2 to alleviate

chronic pain by reversing DNA methylation patterns.

Similarly, histone acetylation has been shown to play an essential role in pain modulation. Histone acetylation typically enhances gene transcription by loosening chromatin structure, whereas histone deacetylation, mediated by HDACs, has the opposite effect. Suppression of HDAC4 activity in spinal neurons has been demonstrated to attenuate pain sensitization and restore normal synaptic connectivity in pain-processing neural circuits [32]. These findings suggest that HDAC4 inhibitors could serve as promising therapeutic agents in the treatment of chronic pain. Several studies have provided additional evidence supporting the role of epigenetic modulation in pain. For example, pharmacological inhibition of HDACs not only reduces pain hypersensitivity but also prevents the development of chronic pain in preclinical models [33]. Similarly, DNMT inhibitors have shown efficacy in reversing established pain phenotypes by reactivating silenced genes involved in nociceptive pathways [34]. Given the accumulating evidence, epigenetic factors such as HDACs and DNMTs represent attractive therapeutic targets for developing novel pain management strategies.

4) Differences in gray matter volume (GMV) and density in chronic pain patients in cortical and sub-cortical regions

Chronic pain results in consistent modifications of GMV and density in the brain [35,36]. It is related to significant GMV decrease in the PFC, insula, thalamus, and ACC. Structural changes and severe brain atrophy were found in patients with pain lasting for a long duration [35,36]. These outcomes define that chronic pain is coupled with neurodegenerative alteration in which prolonged pain reduces the quality of pain-modulating areas [35]. The changes are noted in various areas involving sensory, affective, and evaluative dimensions of pain such as the ACC, insula, PFC and the thalamus, particularly in patients who have fibromyalgia, chronic back pain, and migraine [36].

GMV reductions in regions such as the PFC, ACC, and thalamus have been linked to pain intensity, emotional dysregulation, and cognitive impairments. These structural alterations underscore the profound impact of chronic pain on brain morphology and its potential as a marker for disease progression and therapeutic efficacy [37]. Nowadays, several studies shed light on the changes in GMV and their correlation with chronic pain and their clinical significance in the diagnosis, and treatment of many diseases. Wang et al. [38] used high-resolution T1

structural scans and voxel-based morphometry, and reported a negative correlation between GMV and the frequency of pain crises in 38 pediatric patients with sickle cell disease similar to other chronic pain conditions such as fibromyalgia and irritable bowel syndrome [38]. Particularly, in the subgroup of sickle cell disease patients with poorer quality of life, a reduction in GMV appeared in the parahippocampus. Accordingly, this matter can be used as an endpoint for the evaluation of pain-directed therapies [38].

These alterations are associated with neuronal atrophy, a reduction in the excitatory neurotransmitters, inflammation, and/or excitotoxicity [38]. Furthermore, Li et al. [39] reported a decrease in GMV in the thalamus in patients suffering from frozen shoulder and highlighted its correlation with pain threshold and intensity by using functional and structural magnetic resonance imaging techniques. Also, the dysfunction in thalamocortical functional connectivity can be used as a neurobiomarker for neuropathic pain [39].

(1) ACC

According to the self-organising map of mind resources, the ACC is responsible for the regulation of pain emotions [40]. It has diminished GMV among chronic pain patients. Such alterations correspond to the increase in the rate of pain, emotional disturbances, and pain control [40]. Several studies indicated that pain sensation is enhanced by negative emotions such as anxiety or depression associated with the dysfunction of the immune system *via* the atrophied ACC [40,41]. This creates a vicious cycle in which emotional suffering and pain are both sustained [41]. The ACC, a key region in the brain's pain matrix, is critically involved in regulating the emotional dimensions of pain [40]. The self-organizing map of mind resources highlights the ACC as central to integrating sensory, cognitive, and emotional pain processing, shaping both the perception and behavioral response to pain. In chronic pain patients, diminished GMV in the ACC has been consistently reported, reflecting a neural substrate for increased pain intensity, emotional disturbances, and impaired pain modulation [40]. These structural deficits are thought to exacerbate the chronic pain experience by altering the connectivity and function of pain-regulating networks.

Emotional disturbances, such as anxiety and depression, frequently co-occur with chronic pain and are closely linked to ACC dysfunction. Studies indicate that negative emotions amplify pain perception, partially

through maladaptive changes in the immune system that are driven by atrophied ACC regions [40,41]. This bidirectional relationship creates a vicious cycle in which chronic pain perpetuates emotional suffering, and emotional disturbances, in turn, enhance the sensation of pain [41]. The interplay between the ACC, emotional dysregulation, and immune system dysfunction highlights the complexity of chronic pain as both a neurological and psychosocial condition.

Emerging research further supports the role of the ACC in pain resilience and recovery. For example, interventions targeting ACC activity, such as mindfulness-based therapies, cognitive-behavioral approaches, and neurostimulation techniques, have shown promise in alleviating both pain and associated emotional distress. These findings emphasize the importance of developing integrative treatment strategies that address not only the sensory aspects of pain but also its emotional and cognitive dimensions.

(2) Insula

Several lines of evidence revealed that the insula, implicated in the processing of sensory as well as affective aspects of pain, exhibits decreased GMV in chronic pain states such as fibromyalgia, chronic low back pain, and migraine [39]. GMV reductions in the insula and thalamus in patients with complex regional pain syndrome were correlated to pain intensity, sensory processing, and emotional regulation [39,42]. Also, previous studies employed a combination of fMRI, psychophysical pain thresholds, and validated questionnaires (*e.g.*, pain catastrophizing scale) to assess sensory processing and emotion regulation. These methodologies provide a comprehensive evaluation of the interplay between sensory inputs and emotional responses in chronic pain [43]. By integrating neuroimaging with subjective assessments, researchers can better understand the mechanisms underlying maladaptive sensory and emotional processing in pain conditions, paving the way for more effective interventions [43]. The findings align with evidence that atrophy in the insula impacts emotional and sensory regulation, reinforcing the persistence of chronic pain *via* altered connectivity with other region, including the thalamus and PFC [42].

(3) PFC

The PFC is involved in regulating cognition and modulation of pain. Earlier studies reported that the deficiency in

GMV in the medial prefrontal cortex (mPFC) and dlPFC was associated with a faulty cognitive and emotional control system [41]. A crucial node of multiple brain networks, the dlPFC is a morphologically and functionally diverse area involved in the cognitive, emotional, and sensory processing. Altered activity in the dlPFC is associated with impaired decision-making, heightened emotional distress, and decreased ability to regulate pain in chronic pain conditions. A growing body of evidence indicates that the structural and functional changes in the dlPFC highlight its central role in the neural circuitry of pain, offering a potential target for therapeutic interventions aimed at restoring its function and alleviating chronic pain [44,45]. Because of this, dlPFC exhibits abnormally elevated function in individuals with chronic pain. Additionally, a number of studies have demonstrated that certain chronic aches are linked to a reduction in the left dlPFC gray matter, and that this anatomical abnormality can be reversed with noninvasive stimulation of the left dlPFC [45]. Accordingly, the dlPFC can be a therapeutic target for the treatment of pain as it was found that decreased left dlPFC gray matter is associated with multiple chronic pain conditions.

Furthermore, it is worth mentioning that the dlPFC is expanded in humans in comparison to primates, indicating a role for the dlPFC in complex cognitive processes such as value encoding, attention, creativity, working memory, emotional regulation, and decision-making [45]. Specifically, it shows activation in response to nociceptive stimuli in healthy subjects, or differential activation between chronic pain patients and controls. Its role in pain remains ambiguous: it has been shown to be involved not only in pain suppression, in line with its role in cognitive and emotional control, but also in pain detection [45]. Also, it exhibits either differential activity in chronic pain sufferers compared to controls or activation in response to nociceptive stimuli in healthy people.

Patients with chronic pain, together with a reduced volume of PFC, demonstrate poor decision-making skills, memory, and an inability to manage their own emotions that exacerbate pain [19]. Particularly, mPFC is essential for regulating pain and pain-related attention; its shrunk volume may lead to pathological rumination in chronic pain conditions. Accordingly, cognition-based therapy has been proven efficient for chronic pain due to the re-structure of the pain pathway in the brain [41].

(4) Thalamus and subcortical structures

Multiple sub-cortical regions are implicated in pain. It

was found that there is a decrease in GMV, primarily in the thalamus which is vital in regulating nociceptive information that is sent to cortical zones such as ACC and insula. This atrophy is linked to central sensitization, a process where the mind becomes more active in pain messages that are expected due to increased sensitivity to pain [35]. Loss of thalamic connectivity in chronic pain enhances pain messages to these areas, enhances the activity of sensory inputs, and decreases the brain's inhibitory responses to pain [35]. This disruption has been found to confer pain modulation by enhancing connections between the thalamus and overall cortical areas involved in pain perception, intensifying pain sensitivity and duration. Furthermore, it was revealed that different subcortical areas including the hippocampus and amygdala are affected during chronic pain. Notably, GMV decreases were associated with mood disorders, anxiety, and depression, which often co-occur with chronic pain [46]. Furthermore, it was shown that the hippocampus which plays an essential role in encoding programs for memory and stress reduction, influences pain responses by enhancing memory for aversive stimuli [46]. In chronic pain, the hippocampus enhances its connection with the ACC and PFC for emotional recall of pain events, promoting further chronic pain symptom [1]. It is significantly reduced in size in chronic pain patients, contributing to the persistence of pain, particularly in conditions like fibromyalgia and migraine [47]. In this regard, Mahmut et al. [47] found that chronic migraine patients had reduced hippocampal volumes, which are correlated with pain frequency and duration, highlighting the hippocampus's role in memory and emotional processing [48]. Importantly, subcortical regions, particularly the amygdala and hippocampus, are critical in the formation and maintenance of pain memory. The amygdala modulates emotional and autonomic responses to pain, while the hippocampus is involved in encoding and retrieving pain-related memories. Chronic pain is associated with hyperactivity and altered connectivity in these regions, contributing to the persistence and emotional salience of pain. Understanding these changes provides insight into the role of subcortical structures in chronic pain and their potential as therapeutic targets [49]. Distinct patterns of neuroplasticity are observed across chronic pain conditions. For instance, fibromyalgia is characterized by widespread cortical thinning and altered connectivity in pain-related regions, while OA shows localized structural changes. Migraine and neuropathic pain exhibit unique alterations in functional connectivity and GMV, reflecting condition-specific adaptations. These findings under-

score the importance of tailoring therapeutic approaches to the neuroplastic changes unique to each chronic pain condition [50].

3. Impact of chronic pain on brain morphology

Multiple conditions of chronic pain were reported to have effects on the structural and functional neuroplasticity. For instance, fibromyalgia is linked to decreased GMV in the ACC, insula, PFC, and the hippocampus. More specifically, it was found that the number of observed GMV changes is in harmony with the severity of symptoms such as pain, fatigue, and cognitive impairment [51]. This implies pathology of the neural circuits in sensory, emotional and regulatory domains in fibromyalgia patients [51]. However, there is potential for neuroplasticity-based therapies, including physical activity and cognitive-based methods, to reverse these structural abnormalities, particularly within the PFC and insula [51].

Moreover, neuroimaging studies in OA patients demonstrate that patients have GMV reductions within the PFC, insula, and somatosensory cortex [51,52]. These structural changes lead to central sensitization, an enhanced response of the affected patients to pain stimuli, with minimal peripheral stimulation [51,52]. Further, it was reported that OA is linked to the neuroinflammatory alterations within the CNS, contributing to both musculoskeletal and affective pain aspects, including depression and anxiety [51,52]. Also, previous reports showed that reduced GMV is observed in the ACC, PFC, and insula in chronic migraine. The degree of these reductions is significantly greater in chronic migraine patients. Also, it was revealed that chronic migraine was exacerbated by excessive emotional stress and hippocampal atrophy [50,51]. Researchers used to study pain processing and perception in migraine during pain stimulation, using noxious, visual, or auditory stimuli, and to investigate the relationship of atypical patterns of brain activation associated with migraine.

On the other hand, substantial suppression of neuropathic pain in conditions such as postherpetic neuralgia and brachial plexus injury was identified in multiple regions, including the thalamus, ACC, insula and PFC [42,53]. Such structural changes relate to enhancing pain sensitivity and impairments of affective regulation. GMV changes in the hippocampus and amygdala are related to increased anxiety and depression in patients with neuropathic pain [42,53]. Consequently, chronic pain results in extensive neuroplasticity alteration in the brain's neurons which are involved in pain, mood, and thinking [42,53].

These changes led to increases in the size of the ACC, insula, PFC, and thalamus and amplifications in pain's sensory and affective dimensions, leading to a vicious cycle of chronicity [42,53].

4. Modifications to DMN connectivity and intensity of pain

It is worth mentioning that it is well-known that chronic pain causes significant abnormalities in connection in the DMN, which is dominant in introspection and self-referential reflections. As mentioned above, the PCC and mPFC usually have a lower connection as highlighted in pain intensity in DMN nodes [53]. This loss of connection extracts resources from usual autocentric operations and allocates them to the constant experience of this pain [53]. Chronic pain is associated with disrupted connectivity between pain-related networks (*e.g.*, DMN, SN, and CEN). These alterations contribute to dysfunctional pain modulation, heightened emotional responses, and impaired cognitive function. Understanding these connectivity changes provides critical insights into the neural basis of chronic pain and highlights potential targets for interventions aimed at restoring network balance and alleviating symptoms [54].

In the triple network model, the nodes DMN, SN, and CEN describe this relation [36]. This model showed that when CEN participates in cognitive operations, chronic pain is diminished because elevated processing of pain information occurs at the expense of other cognitive inputs *via* SN activity [36,55]. This is associated with the executive disorder and results in deficits in flexibility metrics and disruption of regulation [55]. Notably, SN is responsible for salient stimuli and decreased connectivity with DMN hubs in chronic pain patients [36,53]. This link also heightens pain attention in which the patient develops a more refined alarm system for the onset of discomfort. Of note, chronic widespread pain has been reported to increase SN connectivity with the anterior insula and superior temporal gyrus, thereby increasing attentional influence on pain [56]. This leads to increased hypothalamic-DMN connectivity with pain, for both pain severity and hypothalamic connectivity responses to the stressor in chronic migraine as compared to healthy controls [53]. This connectivity pattern reinforces pain as a central experience in the DMN's altered functioning [53]. Moreover, the insula plays a central role in integrating sensory and affective pain experiences [53]. In more detail, chronic pain patients exhibit insula hyperactivity that enhances SN-DMN connectivity, increasing attentional

and emotional responses to pain stimuli [53]. This pattern is reported prominently in fibromyalgia, where insula-driven SN-DMN integration aligns with heightened pain sensitivity [57]. In more details, chronic pain also leads to extensive reorganization in cortical and subcortical regions responsible for sensory and emotional pain processing. This includes structural and functional changes in the ACC, amygdala, insula, and S1, all of which contribute to an intensified and emotional experience of pain [57]. Moreover, several studies revealed that the ACC is characterized by increased connectivity with the amygdala and PFC, consistent with emotional sensitization to pain [57]. According to previous research, ACC interaction with S1 and S2 integration of actual and broadly emotional pain reinforces the comprehension of pain as distressing [58,59]. Regarding the amygdala, it is involved in pain. It modulates emotional responses and has a higher augmented connection with the sensory-related cortical areas in chronic pain. This link enables the emotional magnification of pain so that the pain stimuli become an emotionally relevant feature and challenging to dismiss [1,60]. In addition, several lines of evidence have shown that the insula integrates interoceptive signals and links these signals to emotional reactions, magnifying the pain effect in chronic pain patients [59,60]. Some fMRI studies showed that the insula's connection with the ACC is more enhanced in chronic pain, which continue to link an emotional context to pain-related experiences [59,60].

5. Functional interplay across pain processing networks

In chronic pain, the CEN, involved in executive functions, exhibits reduced connectivity with sensory regions [61]. This impairs cognitive control over pain-related thoughts leading to diminished descending modulation of pain [61]. The reduced dlPFC connectivity with sensory networks reflects a decreased capacity for executive pain management, supporting pain's dominant role in patients' thoughts [45]. In addition, it was shown that pain-evoked reorganization impacts functional networks, reducing network efficiency and enhancing sensitivity to pain stimuli [62]. Studies have shown that chronic pain patients experience a decrease in network modularity, leading to inefficiencies and heightened pain sensitivity which reinforces pain persistence [63]. On the other hand, the SN biases attention toward pain, reinforcing pain's salience in daily experiences in chronic pain conditions [64]. Furthermore, it was reported that hypervigilance to pain, driven by SN interactions with the ACC and

insula, magnifies pain's emotional impact and fosters a feedback loop of sustained pain focus [64].

6. Implications for diagnosis and treatment

It is well-established that the structural and functional brain alterations observed in chronic pain provide critical insights into diagnostic and therapeutic possibilities [65,66]. Advances in neuroimaging and functional connectivity analysis have shown that changes in brain morphology such as GMV reduction in critical regions and changes in functional connectivity in networks like the DMN and SN, can serve as biomarkers for chronic pain conditions [65]. Thus, there are therapeutic implications for studying neuronal plasticity. For instance, it was reported that cognitive behavioral therapy (CBT) reduces changes in plasticity and neurostimulation. Also, ketamine can decrease pain by preventing maladaptive plasticity in the ACC [66]. The findings imply that neuroplastic changes in chronic pain patients can be mitigated by non-invasive brain stimulation, neurofeedback, and exercise-based programs [66]. Exercise-based interventions may offset brain volume reduction in chronic pain, as neuroplastic concepts support the recovery of lost brain and cognitive function. For instance, pain control in trigeminal neuralgia patients allows a partial return of the hippocampal volume in cases connected with memory and stress regulation. This implies that appropriate pain treatment could reverse pathological neural structural alterations in chronic pain [67]. On the other hand, it is worth mentioning that GMV and functional connectivity changes has limited specificity as similar changes are observed in other neurological and psychiatric conditions. Integrating neuroimaging with behavioral and clinical data could improve the specificity and utility of these biomarkers [68,69].

7. Diagnostic potential of brain imaging and biomarkers

Neuroimaging has revealed that functional connectivity disruptions, particularly in the DMN, SN, and CEN, correlate with chronic pain severity and symptom persistence. DMN alterations have been studied using fMRI, which shows that chronic pain patients can be distinguished from the healthy population by imaging [52,70]. Accordingly, the more sensitive measure of functional connectivity was suggested as a biomarker for the transition of pain to a chronic state [52,70]. For example, dynamic functional connectivity studies showed that pain

affects the connectivity of brain networks to the theta and gamma range, specifically to the frontal networks associated with emotion and sensation [71]. The chronic musculoskeletal pain diagnosed with functional near-infrared spectroscopy machine learning has been quite consistent with even the chronic pain patients' connectivity pattern [71]. Using patterns of the lowered connection in PFC, the chronic pain neural marker with the increased spontaneous activity has provided a lot of evidence regarding its effectiveness on clinical diagnosis [72]. Additionally, brain stimulation therapies like theta-burst transcranial magnetic stimulation (TMS) targeting the DMN and PFC showed promising results for diagnosis and treatment, particularly in conditions like knee OA [72,73]. To add, the results of TMS imply that alterations in functional connectivity in chronic pain can enhance diagnostic precision and pain relief [73].

8. Therapeutic applications of brain connectivity insights

Multiple studies revealed that neurotechnologies like transcranial direct current stimulation (tDCS) and TMS can restore connectivity in affected networks in chronic pain, especially within the regions of ACC, insula, and PFC [74]. Chronic pain patients can benefit from tDCS which reduces abdominal pain in the patients of inflammatory bowel disease and restores abnormalities in functional connectivity [74]. Neurofeedback and brain computer interfaces are considered another line of therapeutic application [71,74]. Abnormal coherence between sources of theta and gamma bands in rest-state electroencephalogram (EEG) could be targeted by non-invasive brain modulation strategies [71]. Also, real-time operations attempting to alter the innate morphology of the brain's network, such as neurofeedback, are also used. For some patients, this may be beneficial especially for controlling pain perceived in the PFC area [40]. Furthermore, Kaplan et al. [75] found that DBS or localized TMS which target insula activity that has connectivity in chronic pain, like fibromyalgia, could decrease the level of pain. These primary hubs in the information network may serve as good targets for patients with some types of chronic pain. On the other hand, neuroplasticity and neuroinflammation are considered hallmarks of chronic pain conditions. Research targeting glial activation suggests potential for reducing pain through anti-inflammatory interventions that lower neuroinflammation which is linked to pain intensity and emotional distress [76]. Accordingly, medications inhibiting microglial activation or

targeting neuroinflammatory pathways offer promising therapeutic avenues. A plethora of evidence has shown that various therapeutic interventions induce brain changes in chronic pain patients. For instance, opioids modulate DMN connectivity and influence reward processing circuits [77] while ketamine alters connectivity in the thalamic and prefrontal regions, providing rapid analgesic effects [78]. Furthermore, spinal cord stimulation modifies somatosensory and affective networks, offering relief in refractory pain conditions [79]. Meanwhile, it was implicated that CBT and exercise-based interventions restore GMV and normalize functional connectivity, highlighting their role in reversing maladaptive neuroplasticity [80,81].

9. Future directions and limitations

Although neuroimaging biomarkers hold promise, there are barriers that include sensitivity, specificity, and cross-population validation. Further research is necessary to standardize imaging methods and validate biomarkers across diverse clinical populations to ensure reliability and utility [52]. Additionally, advances in multi-modal imaging, integrating fMRI, EEG, and positron emission tomography can reveal comprehensive brain network alterations. Longitudinal studies may further distinguish between transient pain responses and sustained pain connectivity changes, enhancing diagnostic precision and guiding interventions tailored to specific pain types.

CONCLUSIONS

Chronic pain induces neuroplasticity that is manifested as gray matter reduction and altered connectivity in key pain-processing areas such as the ACC, insula, PFC, and thalamus. Other sub-cortical regions are also involved including the thalamus and hippocampus. These changes disrupt sensory and emotional processing and reinforce pain perception through maladaptive feedback loops within neural networks. Critical networks like the CEN, DMN and SN are reorganized, leading to persistent, heightened awareness of pain and emotional distress. Also, structural and functional changes in brain connectivity patterns offer valuable diagnostic and therapeutic insights for chronic pain management. Leveraging these changes as diagnostic markers can refine pain assessment. Targeted therapies based on neuroplasticity and connectivity adjustments offer promising routes to alleviate pain. Moreover, neuroimaging biomarkers that detect

brain changes in chronic pain syndromes can improve diagnostic efficacy. However, additional research is needed to define these methods and their biomarkers for the future use in clinical medicine.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Sahar M. Jaffal: Writing/manuscript preparation.

ORCID

Sahar M. Jaffal, <https://orcid.org/0000-0001-7115-5841>

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