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Cortico-limbic pain mechanisms.

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Abstract

Pain has a strong emotional component and is defined by its unpleasantness. Chronic pain represents a complex disorder with anxio-depressive symptoms and cognitive deficits. Underlying mechanisms are still not well understood but an important role for interactions between prefrontal cortical areas and subcortical limbic structures has emerged. Evidence from preclinical studies in the rodent brain suggests that neuroplastic changes in prefrontal (anterior cingulate, prelimbic and infralimbic) cortical and subcortical (amygdala and nucleus accumbens) brain areas and their interactions (corticolimbic circuitry) contribute to the complexity and persistence of pain and may be predetermining factors as has been proposed in recent human neuroimaging studies.

Introduction

Compelling evidence from clinical neuroimaging studies points to an important role of the corticolimbic system in the development, amplification and prediction of chronic pain and its emotional-affective dimension [4, 146]. These corticolimbic brain areas include primarily the medial prefrontal cortex (mPFC), amygdala, nucleus accumbens and hippocampus. Closely related brain areas interacting with limbic circuity such as anterior cingulate cortex (ACC) and insular cortex (IC) have consistently been implicated in acute pain and some forms of chronic pain [164].

Here we review information from preclinical mechanistic studies on neuronal activity and synaptic changes in the (medial) prefrontal cortex and interconnected limbic areas (amygdala, nucleus accumbens/striatum and hippocampus) as pain mechanisms. We also provide clinical context for the preclinical literature by discussing related studies in human subjects.

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Competing interests

There are no conflicts of interest.

Prefrontal cortical (PFC) pain mechanisms

The prefrontal cortex is an important neural substrate for executive functions and decision-making; reduced PFC function leads to increased impulsivity, reduced control over social behaviors, and impaired decision making. It is a heterogeneous brain region composed of multiple structures and exhibits species-specific differences between rodents, primates, and humans in connectivity, cytoarchitecture, electrophysiological properties, protein expression, and responses following damage [58, 115, 119]. The rodent nomenclature, including the infra- and pre-limbic and anterior cingulate cortices, will be used in this review. These are thought to correspond to Brodmann areas 25, 32 and 24b, respectively, in primates [151]. Cortical areas other than the PFC, such as the IC, have been implicated in pain processing and pain modulation, including through limbic regions [71, 72, 137], but will not be discussed in detail in this review.

Prelimbic and infralimbic mPFC

The mPFC has emerged as a critical region for top-down cognitive control over emotion-driven behaviors via processes including fear conditioning and extinction. The prelimbic and infralimbic mPFC receive inputs from regions including the thalamus, basolateral amygdala (BLA), hippocampus, and contralateral mPFC [58, 84, 93, 94]. A portion of BLA inputs terminate on GABAergic interneurons, allowing for feedforward inhibition of mPFC output (see Fig. 1) through modulation of mPFC projection neurons [43, 57, 58, 118]. Both the prelimbic and infralimbic cortices send excitatory projections to the amygdala [43, 58, 108, 109, 112, 118, 144]. The prelimbic mPFC predominately targets the BLA, whereas the infralimbic cortex projects to BLA and other amygdala divisions including the lateral amygdala (LA), intercalated cell mass of the amygdala (ITC), and possibly to the lateral central nucleus of the amygdala (CeL). It is the projection to the ITC, directly or indirectly via BLA, that is thought to be important in fear extinction [43, 58, 118]. The ITC sends GABAergic projections to central amygdala (CeA) projection neurons, allowing for feedforward inhibitory control of amygdala output by the mPFC (see Fig. 1). See Figure 2 for a diagrammatic representation of prefrontal cortical neurocircuitry and its interactions with other cortical and subcortical structures.

Chronic pain has been proposed to be “persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury” [4]. Given its importance in extinguishing subcortically-driven fear behaviors, it seems reasonable to hypothesize that pain-related loss of mPFC activation could contribute to pain chronification. Indeed, chronic pain is thought to engage similar brain mechanisms as fear extinction [44, 47], and preclinical evidence in acute and chronic pain models has emerged that supports the idea of pain-related cognitive impairment via feedforward inhibition and resultant loss of cortical control over subcortical responses.

Preclinical evidence suggests that mPFC function is impaired in the pain state. Electrophysiology studies in the anesthetized rat demonstrated decreased evoked and background activity in the prelimbic [75] and infralimbic [73] mPFC in acute arthritis pain. In layer V prelimbic mPFC neurons, the spared nerve injury (SNI) model of neuropathic pain resulted in reduced glutamatergic transmission [79] and reduced pyramidal cell firing

[163] in brain slice physiology experiments. Accordingly, spontaneous excitatory postsynaptic currents (EPSCs) were reduced in frequency, which corresponded to a reduction in electrically evoked EPSCs [79]. Length and branching of apical dendrites and glutamate concentration in the mPFC were reduced in SNI rats compared to controls. This reduction in neuronal activity was mediated by increased feedforward inhibition from parvalbumin (PV) expressing GABAergic interneurons [79]. In addition, modulatory effects of acetylcholine (ACh) neurotransmission were altered in the SNI model of neuropathic pain [123]. Under normal conditions, ACh increased excitability of layer V prelimbic pyramidal mPFC neurons in brain slices through activation of postsynaptic M1 receptors. In the SNI model, however, this effect was lost due to M1 receptor internalization, suggesting that M1 receptor plasticity and subsequent alterations in cholinergic neurotransmission contribute to pain-related mPFC dysfunction.

Taken together, these data support reduced activity of layer V mPFC neurons in acute and chronic pain states. Reduced mPFC activity has been linked mechanistically to pain behaviors in a series of experiments using manipulations of mPFC activity. Optogenetic activation of layer V prelimbic mPFC neurons in SNI rats significantly inhibited tonic pain responses in the conditioned place preference test and mechanical and thermal sensitivity on the von Frey and Hargreaves tests, respectively [90]. Importantly, pain-related anhedonic and behavioral despair depression-like behaviors were reduced with mPFC activation on the sucrose preference (SPT) and forced swim (FST) tests, respectively. Similar behavioral effects were observed by manipulation of interneurons involved in feedforward inhibition of prelimbic pyramidal cell output. Optogenetic silencing of PV expressing GABAergic interneurons in SNI rats decreased tonic pain responses and mechanical and thermal sensitivity, whereas optogenetic activation exacerbated SNI-associated tonic pain and mechanical and thermal sensitivity [163]. These studies provide a causal link between mPFC activity and pain behaviors, and show the importance of GABAergic interneuron activity for the regulation of mPFC output. Manipulating activity of these interneurons could therefore be a therapeutic strategy for chronic pain.

Mechanisms underlying mPFC deactivation in the pain state are an area of active investigation, but altered inputs from the amygdala appear to play a role. Increased feedforward inhibition driven by glutamatergic BLA projections to the mPFC was observed in the infralimbic cortex in the arthritic pain model [82]. The enhanced BLA-driven synaptic inhibition of layer V pyramidal cells was reduced following pharmacologic restoration of postsynaptic metabotropic glutamate receptor 5 (mGluR5) and presynaptic cannabinoid receptor 1 (CB1) function. This rescue strategy decreased mechanical sensitivity, inhibited nocifensive and averse affective pain behaviors, and restored decision-making on the rodent gambling task [82].

Similar to BLA-driven infralimbic mPFC deactivation, increased activity of BLA neurons projecting to the prelimbic mPFC was found in anesthetized rats after acute arthritis pain induction [75], which corresponded to reduced prelimbic pyramidal cell activity through a mechanism dependent on presynaptic mGluR1 [75, 140]. This effect was due to enhanced feedforward inhibition from the BLA, whereas excitatory inputs did not change. Blockade of BLA hyperactivity with a CRF1 receptor antagonist restored responsiveness and background

activity of prelimbic mPFC output neurons to near pre-arthritis levels and inhibited mechanical hypersensitivity, nocifensive and averse affective pain behaviors, as well as restored decision-making on the rodent gambling task [75]. Reduced prelimbic mPFC output was also observed in a neuropathic pain model (SNI) due to feedforward inhibition of layer V pyramidal cells from PV-expressing interneurons [163]. As the BLA projects to these cells [74, 108, 144], this provides further evidence for pain-related BLA-mediated deactivation of prelimbic mPFC output.

These studies support an important role of amygdala-driven deactivation of layer V mPFC output neurons in pain states. Mechanistically, they point to a contribution of CRF, mGluR5, and CB1 to feedforward inhibition of mPFC output by PV-expressing interneurons in the prelimbic, and possibly infralimbic, mPFC. In contrast, there is evidence for layer II/III pyramidal cell hyperexcitability in pain states. In the SNI model, basal dendrite spine density in layer II/III prelimbic mPFC neurons is increased in SNI rats compared to sham controls [101]. The morphological change was accompanied by an increase in N-methyl-D-aspartate (NMDA) receptor-mediated currents and NMDA/AMPA ratio in brain slices, which correlated with increased mechanosensitivity in the von Frey test. Enhanced glutamatergic transmission and excitability of layer II/III prelimbic pyramidal cells were found in the SNI model as the consequence of a hyperpolarizing shift in activation of the cationic hyperpolarization-activated cyclic nucleotide-gated (HCN) channel current, which is indicative of a reduction in open channel probability causing a reduction in the HCN mediated cationic Ih current [38]. Pharmacological HCN channel blockade attenuated cold but not mechanical hypersensitivity in SNI rats [38]. Voltage-dependence of HCN channel activation is regulated by noradrenergic afferents, and intra-mPFC infusion of an α2 receptor agonist had analgesic effects in an SNI model [37], suggesting a role for aberrant pain-related noradrenergic transmission in the prelimbic mPFC. An mGluR1/5 agonist facilitated firing in prelimbic layer V mPFC neurons in the SNI model compared to sham controls [38], and blockade of prelimbic mGluR5 attenuated mechanical hypersensitivity and depression-like behaviors [35], suggesting a role for mGluR5 in these effects. Similarly, increased frequency and amplitude of spontaneous EPSCs were recorded in layer II/III prelimbic pyramidal cells in the complete Freund's adjuvant (CFA) inflammatory pain model [152]. However, this synaptic change corresponded to a decrease in excitability. In fact, optogenetic activation of these neurons had antinociceptive and anxiolytic-like effects in the CFA model, and optogenetic inhibition of these neurons under normal conditions was anxiogenic [152]. Decreased excitability and behavioral effects were linked mechanistically because both were mitigated by shRNA-induced knockdown of cyclin-dependent kinase 5 (Cdk5).

Anterior cingulate cortex (ACC)

The ACC is a limbic structure that is thought to contribute to affective/motivational rather than sensory/discriminative aspects of pain [18, 105, 108, 109], but see [33]. ACC neurons have bilateral and large receptive fields [160], suggesting they do not provide discriminatory sensory information. The ACC receives nociceptive information from the medial thalamus [105], which allows for ACC contributions to pain processing. Neuroimaging studies demonstrate ACC activation following the offset of a painful thermal stimulus in both rats [18, 85] and humans [18], and these responses were significantly attenuated by

intraperitoneal (i.p.) injection of morphine in rats [85, 153]. This nociceptive information is integrated with motivational and affective information received from IC, mPFC and BLA inputs to generate ACC-mediated pain responses [7, 25, 105, 144, 154]. Consistent with this, microinjection of excitatory amino acids into the ACC is sufficient to induce avoidance learning without the need for a noxious stimulus, blockade of excitatory amino acid receptors in the ACC is sufficient to block avoidance learning from a peripheral noxious stimulus, and lesioning of the ACC after conditioning did not affect avoidance learning [77]. The ACC generates these affective and motivational pain responses via projections to the amygdala, NAc, and mPFC [7, 8, 25, 105, 108, 144, 154].

Preclinical studies mechanistically link the ACC to pain processing and pain modulation. Bilateral chemical lesioning of the ACC in rodents abolished supraspinally organized but not spinally organized pain behaviors induced by injection of bee venom into the paw [124]. Optogenetic activation of inhibitory neurocircuitry in the ACC resulting in reduced ACC output inhibited pain responses in the formalin test [59]. Phosphorylation of cAMP response element-binding protein in the ACC, which is thought to be related to pain memory, as well as phosphorylated PKA was increased in rats after two intraplantar injections of carrageenan, which was subsequently reduced by electroacupuncture but not indomethacin [133, 141]. This intervention corresponded to a reduction in pain behaviors. In a chronic neuropathic pain model (spinal nerve ligation model, SNL), bilateral electric lesioning of the ACC significantly decreased escape/avoidance behavior, but did not affect anxiety responses or mechanical sensitivity [56, 89]. In addition, increased levels of c-Fos, a general marker of neuronal activation, after unilateral intraplantar carrageenan injection were directly related to escape/avoidance behavior but not to mechanical sensitivity of the affected paw [56, 145].

Mechanistically, these effects could be due to interactions with pain neurocircuitry in the periaqueductal gray (PAG). The ACC and PAG are among the structures that are activated in anticipation of a noxious stimulus in human subjects [25], and increased negative emotion is associated with activation of ACC-PFC-PAG circuitry [25, 150] and increased activity in the ACC [25]. In a preclinical study, electrical stimulation of the ACC rescued escape/avoidance behavior but not mechanical sensitivity, and this effect was significantly reduced following PAG lesions [56]. Mu opioid receptors are thought to be important for this interaction and for pain modulation by the ACC. In clinical studies of the placebo effect from expectation of pain relief, an opioid antagonist (naloxone) decoupled ACC and PAG activity as well as reduced the effect of placebo analgesia [25, 46]. In a preclinical study, beneficial effects of low dose systemic morphine on affective escape/avoidance behaviors were mimicked by stereotaxic injection into the ACC [56, 86-88, 107].

These studies support an important role of the ACC in mediating affective/motivational aspects of pain, and point to ACC-PAG interactions and mu opioid receptors as important mechanistic contributors. However, a recent study suggests that selective optogenetic activation or silencing of ACC-spinal cord projecting neurons causes mechanical hypersensitivity or antinociception, respectively, through direct activation of excitatory spinal dorsal horn neurons [33].

Amygdala

The amygdala is a limbic brain structure involved in emotions and affective disorders [108, 109, 112, 144, 156]. Identification of a nociceptive input via the spino-parabrachio-amygdaloid pathway, clinical neuroimaging data showing amygdala activation in experimental and clinical pain states, as well as preclinical studies showing maladaptive plasticity and hyperactivity in the pain state have implicated the amygdala as a critical node in emotional affective aspects of pain [47, 108, 109, 135, 136, 144, 146, 147]. Aberrant amygdala function also increases risk of developing chronic pain as increased white matter connectivity within the mPFC-amygdala-hippocampus circuit and reduced amygdala size are independent risk factors for persistence of back pain [147]. The focus of this section is on pain-related amygdala changes and cortico-amygdala interactions. Information about molecular level pain-related amygdala plasticity and therapeutic strategies targeting this plasticity can be found in recent review articles [105, 144, 156].

The amygdala receives cortical (mPFC, ACC, and IC) and thalamic inputs that provide polymodal sensory information to the lateral/basolateral amygdala (LA/BLA) complex [108, 109, 144]. The LA/BLA attaches emotional and affective context to this sensory information, which is transmitted to the CeA for further processing and output to brain centers of behavioral modulation. The BLA also projects to the cortical areas that provide information to the amygdala and exert control functions. Projections to the mPFC in particular are involved in pain-related cognitive dysfunction and in fear conditioning [83, 108, 144], and preferentially target cortico-PAG projection neurons in layer V of the infralimbic cortex and cortico-amygdalar projection neurons in layer II of the prelimbic cortex [34].

The CeA is predominantly composed of GABAergic neurons and serves major output functions for amygdala fear and pain neurocircuitry [108, 109, 144]. Purely nociceptive sensory information is conveyed to the lateral and capsular division(s) of the CeA (CeLC) via the spino-parabrachio-amygdaloid tract from the parabrachial (PB) nucleus (external lateral division). This nociceptive projection also engages feedforward inhibition from interconnected GABAergic interneurons within the CeA [139]. PB input is integrated with polymodal sensory information from the BLA to generate amygdala-mediated pain responses [108, 109, 144]. The medial division of the CeA (CeM) and corticotropin releasing factor (CRF) positive neurons in the lateral CeA serve amygdala output functions, and project to the hypothalamus, other limbic structures, and brainstem regions involved in behavioral expression such as PAG and PB. The CeL can also influence output from the CeM by way of reciprocally connected GABAergic interneurons in the CeA, although this inhibitory neurocircuitry has not yet been well described for amygdala pain mechanisms [36, 43, 49, 66].

The ITC is a region interposed between the CeA and BLA that receives excitatory cortical input from the infralimbic mPFC, as well as input from the BLA [108, 109, 144]. The ITC then sends GABAergic projections to the CeL, allowing for feedforward inhibition of amygdala output though a neuropeptide S (NPS)-dependent mechanism [60, 78, 91, 92, 100, 117, 126, 159]. It is this feedforward inhibition driven by cortical inputs, directly or

indirectly via BLA, that has been implicated in fear extinction pathways [43, 108, 109, 118, 144]; dysfunction of this input has been associated with impaired fear extinction [32, 67, 81, 134, 156].

Preclinical *in vivo* and brain slice physiology studies have identified pain-related dysfunction of this neurocircuitry, resulting in increased neuronal activity and enhanced excitatory synaptic transmission in the pain state. Neuronal excitability is increased in the CeA in acute arthritis [20, 55, 108, 111, 144, 149] and neuropathic [69, 104] pain models, as well as in the BLA [75] in an acute arthritis pain model. In addition, excitatory synaptic transmission at the PB-CeL and BLA-CeL synapses [20, 55, 63, 110, 127], as well as the LA-BLA synapse [75] is enhanced in the acute arthritis pain state. Interestingly, the degree of synaptic potentiation at the PB-CeL synapse occurs through a mechanism involving C-fiber afferents [104] and correlates to the degree of mechanical hypersensitivity in neuropathic pain [69]. It should be noted that the PB input is uniquely characterized by its content of calcitonin gene-related peptide (CGRP), and CGRP receptor activation in the CeLC is critically involved in pain-related plasticity [39, 62-64, 69, 114].

Interactions between the BLA, infralimbic mPFC, and ITC have emerged as important mediators of pain-related dysfunction of cognitive control of amygdala output in the pain state. Synaptic activation of ITC cells [126] and subsequent inhibition of CeL activity [126, 127] is reduced in the acute arthritis pain state. Decreased activity of infralimbic mPFC projection neurons (see Prelimbic and infralimbic mPFC; [75, 144, 156]) accounts for decreased ITC-mediated feedforward inhibitory control of CeL activity, and thus for decreased cognitive control of amygdala output. In line with this, pharmacological activation of infralimbic mPFC CB1 and mGluR5 in the arthritis pain state but not under normal conditions increased evoked and background activity in the anesthetized rat in the infralimbic mPFC and inhibited responses in the CeL [73].

Dysfunction in the interaction between amygdala and cortical control centers such as mPFC has emerged as a key element of acute and chronic pain-related plasticity in the brain, and is thought to be a significant node in the emotional affective dimension of pain and in pain-related cortical dysfunction as well as a predictor of pain vulnerability [146, 147]. Details and pain-related plastic changes in individual elements of the underlying neurocircuitry remain to be determined. Current work in the field focuses on neurochemically and molecularly distinct neurons and synapses in different amygdala regions, their inputs and projection targets, using transgenic, opto- and chemogenetic techniques, which makes the amygdala a model system for the study of brain mechanisms of pain and may help identify new molecular targets and therapeutic strategies for future translational studies.

Nucleus accumbens

The nucleus accumbens (NAc) is a forebrain structure that is involved in reward pathways and integrates cortical and affective information in order to assign motivation and value for selection of appropriate behavioral responses to outside stimuli [2, 4, 7, 8, 52, 70, 102, 129]. Dysfunctions of brain neurocircuitry involved in assigning salience [15, 16, 19, 22, 25] and

value [23, 48, 157] are thought to be involved in the transition to chronic pain. The NAc has emerged as an important mediator of this pain-related dysfunction.

The NAc is widely considered to be made up of a shell subregion and a lateral core section [10, 52, 161]. These regions are distinguished by their connectivity to cortical and subcortical regions [10, 52]. In addition, the NAc shell is thought to evaluate impending pain and utilize spatial information from the hippocampus for appetitive learning, and the core activates with expectation of relief of an aversive stimulus and signals the reward value of pain cessation, as well as utilizes information from the BLA for appetitive learning [10, 52, 70, 125]. A diagram of NAc circuitry is included in Figure 2.

Neuroimaging studies have implicated NAc in acute and chronic pain responses. In freely moving rats, decreased NAc activity was observed with thermal [17, 21] and electrical [96] noxious stimuli. Dopamine levels are reduced in the NAc in SNI rats [125] and mechanistically, SNI involves upregulation of GABAergic indirect spiny projection neurons (iSPN), which is related to mechanical hypersensitivity [125]. These deficits were overcome by supplementing dopamine levels with L-DOPA in combination with either naproxen or a D2/D3 receptor agonist, suggesting a role for altered dopamine neurotransmission in these effects and implicating dopamine modulation as a therapeutic strategy for pain [125].

Alterations of NAc circuitry and connectivity have been identified as independent risk factors for development of chronic pain [3, 147]. Connectivity between the NAc and PFC is predictive of progression to chronic pain in patients presenting with low back pain [3, 11, 65, 125, 146, 147]. This was accompanied by decreased gray matter density in the NAc in patients that went on to have persistent back pain [11], and the degree of connectivity was related to underlying spontaneous pain [65]. In addition, fractional anisotropy in the NAc was correlated with that in the mPFC in patients that recovered from subacute back pain, but not in those in whom pain persisted [97].

Several preclinical and clinical studies have implicated reward circuitry and stimulus valuation and salience circuitry, including the NAc, in pain plasticity [2-4, 7, 9, 11, 18, 47, 65, 105, 106, 125, 146, 147, 157]. Pain-related changes in NAc cortical connectivity have emerged as one of the known risk factors for transition from acute to chronic pain [3, 11, 146, 147]. Convergence of pain relief and reward mechanisms is a relatively new and exciting area of pain research. Therapeutic strategies to correct those deficits remain an area for further investigation.

Cortico-hippocampal interactions

The hippocampus is a limbic brain region that is well known for its role in declarative and episodic memory [13, 45]. This is based on findings in humans that hippocampal damage results in amnesic effects [132], as well as findings in rodents that hippocampal lesions result in impaired performance on memory tasks such as the Morris water maze and recognition of sequences of events [13, 53, 80, 98, 99].

The hippocampus has also emerged as a critical node in emotionality, particularly for anxiety and depression [13, 95, 103]. Hippocampal deficits are observed in alcoholism and

neuropsychiatric disorders [13, 51, 54, 95]. Hippocampal volume is decreased in human subjects with depression, and smaller volumes could convey increased risk for depressive disorders [31, 95, 113]. Electroconvulsive treatment results in improvement of depressive symptoms and increases hippocampal volume [24, 95]. It has been suggested that anti-depressant drugs exert their effects through increased neurogenesis in the dentate gyrus of the hippocampus [13, 131]. Hippocampal lesions improve anxiety-like behaviors in rats [13, 40]. The hippocampus is also an important brain region in fear contextualization, conditioning, and extinction [1, 12-14, 120, 130, 155, 162] and subjects with larger hippocampal volume show higher fear contingency awareness [26].

The hippocampus is closely interconnected with other limbic and cortical brain regions involved in emotion and cognition. The hippocampus is composed of the Cornu Ammonis (CA1-3) and the dentate gyrus (DG), where hippocampal neurogenesis is thought to occur [148]. It is also organized into dorsal and ventral subregions [138]; the dorsal hippocampus is thought to be involved in cognitive processes, including spatial memory and learning, and the ventral hippocampus in emotion [148]. The ventral hippocampus receives limbic input from the BLA [50, 121]. It also receives indirect input from the mPFC, which is thought to be important for episodic memory and context retrieval [76, 158]. Direct hippocampal projections from the ventral hippocampus to the prelimbic and infralimbic mPFC may be important for expression of anxiety and memory contextualization [68, 116, 122, 142]. The ventral hippocampus also sends excitatory projections to the NAc, which has been shown to drive depression-like behaviors in a chronic stress model [6]. See Figure 2 for a diagram of this cortico-limbic circuitry.

Pain is frequently associated with aversive emotional states and memory deficits. In a murine model of Complex Regional Pain Syndrome (CRPS), mice demonstrated anxiety-like behaviors, mechanical hypersensitivity, and impaired working memory [143]. Rats with SNI-induced neuropathic pain also have short term memory deficits, which corresponded to increased interleukin-1 beta (IL-1β) in the sciatic nerve, serum, PFC, NAc, amygdala, and hippocampus [61]. Interestingly, levels of IL-1β correlated to mechanical withdrawal thresholds in rats with SNI-induced neuropathic pain but not sham controls, implying a direct relationship between enhanced pain-related expression and nociception [41, 42]. Hippocampal plasticity could contribute to both memory and averse affective deficits in the chronic pain state.

In line with this, several studies have demonstrated hippocampal involvement in pain. Spatial encoding by hippocampal place cells is altered in CA1 following SNI in freely moving rats [30]. SNI mice demonstrate learning and memory deficits [103, 128], which corresponds to decreased hippocampal extracellular signal-regulated kinase (ERK) expression and phosphorylation, reduced neurogenesis, and altered synaptic plasticity [103]. Interestingly, increased hippocampal neurogenesis and related hippocampal learning mechanisms may be involved in the development of persistent pain because impairing neurogenesis reduced emergence and/or severity of pain behaviors [5]. However, specific mechanisms of these effects and causal relationships between altered neurogenesis and pain have not yet been established. Mechanistically, short term plasticity and long term potentiation at the CA3-CA1 synapses were impaired, density of presynaptic boutons in

CA1 synapses was reduced, and tumor necrosis factor alpha (TNF-α) levels were increased in cerebrospinal fluid, plasma, and the hippocampus in a neuropathic pain mouse model (SNI) [128]. Intrahippocampal injection of TNF-α in naïve rats mimicked the behavioral effects associated with SNI, whereas deletion of the TNF receptor 1 in SNI rats prevented their development, suggesting a role for neuroinflammation in these effects.

Changes in cortico-hippocampal and intrahippocampal interactions have been observed in chronic pain. SNI pain reduces information flow in the mPFC-dorsal CA1 circuit and increases fronto-hippocampal theta entrainment which is inversely related to performance on a spatial working memory task in the freely moving rat [29]. Within the hippocampus, dysregulation of dopamine transmission has been implicated in chronic pain. Freely moving SNI rats lacked the extent of increased dorsal CA1 firing rate present in sham rats when deciding between potential reward locations in a figure-8 maze and had reduced theta phase coherence and dorsoventral connectivity compared to sham animals [28]. This corresponded to increased dopamine D2 receptor and decreased D3 receptor mRNA expression in the dorsal hippocampus, as well as increased D1 receptor, D2 receptor, and tyrosine hydroxylase and decreased D3 receptor mRNA expression in the ventral hippocampus. Systemic application of a D2/D3 receptor agonist reversed electrophysiological and memory but not pain-related behavioral deficits in SNI rats. These deficits were exacerbated by systemic administration of a D2 receptor antagonist, which was related to a selective disruption of hippocampal theta oscillations and decrease in intrahippocampal CA1 connectivity [27]. This set of data suggests that cortico-hippocampal interactions are altered in the pain state, and that modulation of dopamine neurotransmission could be involved in these effects.

Accumulating evidence suggests that the hippocampus is involved in chronic pain. Functional and structural changes in the hippocampus and in hippocampal connectivity to other limbic or cortical structures could contribute to learning and memory deficits, as well as to aversive cognitive and affective states associated with chronic pain.

Conclusions

Chronic pain has significant emotional affective and cognitive components, which contribute to its morbidity. Patients with chronic pain have increased risk for neuropsychiatric conditions such as anxiety and depression, as well as cognitive deficits including impaired decision-making and memory. Mechanisms of persistent pain and its complex emotional affective and cognitive components are not well understood, but it is intuitive to focus on the limbic system and corticolimbic interactions as key players. Convincing evidence suggests that changes in cortical (mPFC and ACC) and subcortical (amygdala and nucleus accumbens) brain regions, as well as the hippocampus, and their interactions contribute to emotional affective and cognitive aspects of pain and pain modulation. Importantly, changes in these circuits are associated with the development of persistent pain and may have predictive value for pain vulnerability. Improving understanding of the neurobiological basis of pain-related changes in these brain regions will provide the knowledge basis required for the development of novel limbic-based therapeutic targets for chronic pain management or even prevention.

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List of abbreviations

ACC	Anterior cingulate cortex
ACh	Acetylcholine
BLA	Basolateral amygdala
CB	Cannabinoid receptor
Cdk5	Cyclin-dependent kinase 5
CeA	Central nucleus of the amygdala
CeL	Lateral division of the CeA
CeM	Medial division of the CeA
CFA	Complete Freund's adjuvant
CA	Cornu Ammonis
CRF	Corticotropin releasing factor
CRPS	Complex regional pain syndrome
DG	Dentate gyrus
EPSC	Excitatory postsynaptic current
FST	Forced swim test
ERK	Extracellular signal-regulated kinase
HCN	Hyperpolarization-activated cyclic nucleotide–gated channel
IC	Insular cortex
IL	Interleukin
i.p.	Intraperitoneal
IPSC	Inhibitory postsynaptic current
ITC	Intercalated cell mass of the amygdala
iSPN	Indirect spiny projection neuron
LA	Lateral amygdala
LA/BLA	Lateral/basolateral amygdala nuclei

mGluR	Metabotropic glutamate receptor
mPFC	Medial prefrontal cortex
NAc	Nucleus accumbens
NMDA	N-methyl-D-aspartate
NPS	Neuropeptide S
PAG	Periaqueductal gray
PB	Parabrachial nucleus
PV	Parvalbumin
SPT	Sucrose preference test
SNI	Spared nerve injury
SNL	Spinal nerve ligation
TNF-α	Tumor necrosis factor alpha
VTA	Ventral tegmental area

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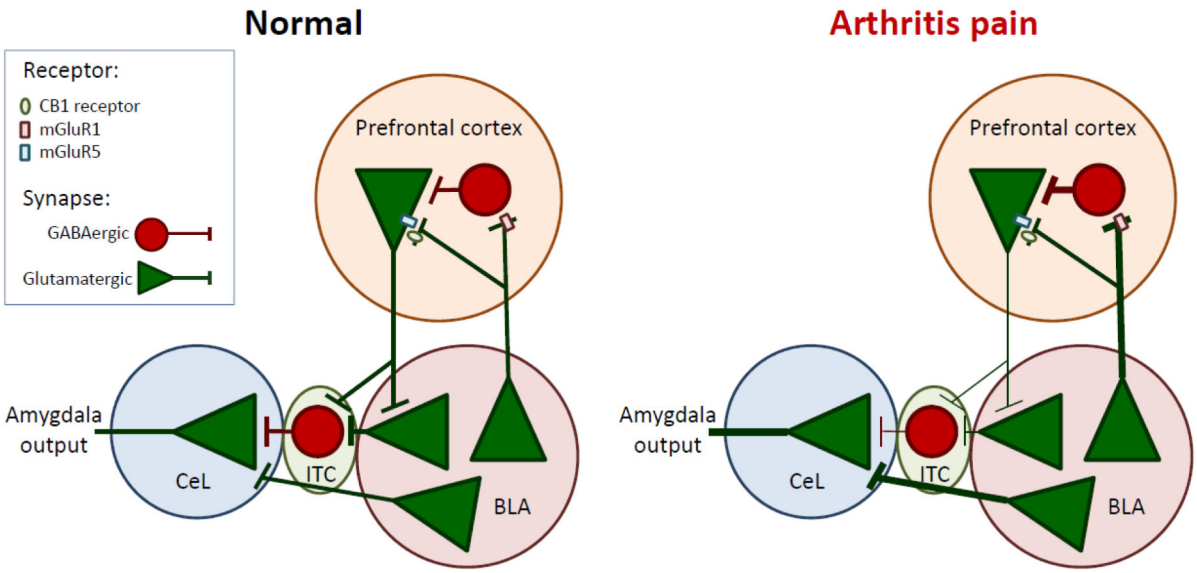

Figure 1. Pain-related changes in cortico-amygdala interactions.

Projection neurons in the BLA synapse on PV-GABAergic interneurons as well as on mPFC projection neurons in the infra- and pre-limbic cortices through a mechanism involving mGluR1, mGluR5, and CB1. PV-GABAergic interneurons in turn project to mPFC projection neurons, resulting in BLA-driven feedforward inhibition of mPFC projection neuron activity. BLA activity is increased in arthritis pain, resulting in pain-related cortical dysfunction. Projection neurons from the infralimbic cortex synapse on BLA projection neurons, as well as GABAergic ITC neurons. GABAergic ITC neurons and BLA projection neurons synapse on CeL projection neurons. Reduced cortical drive onto BLA and ITC neurons in the arthritis pain state results in reduced feedforward inhibition onto CeL projection neurons. This, coupled with increased drive from the BLA, results in pain-related amygdala hyperactivity. mPFC, medial prefrontal cortex; CB1, cannabinoid receptor 1; mGluR, metabotropic glutamate receptor; CeL, lateral division of the central nucleus of the amygdala; ITC, intercalated cell mass of the amygdala.

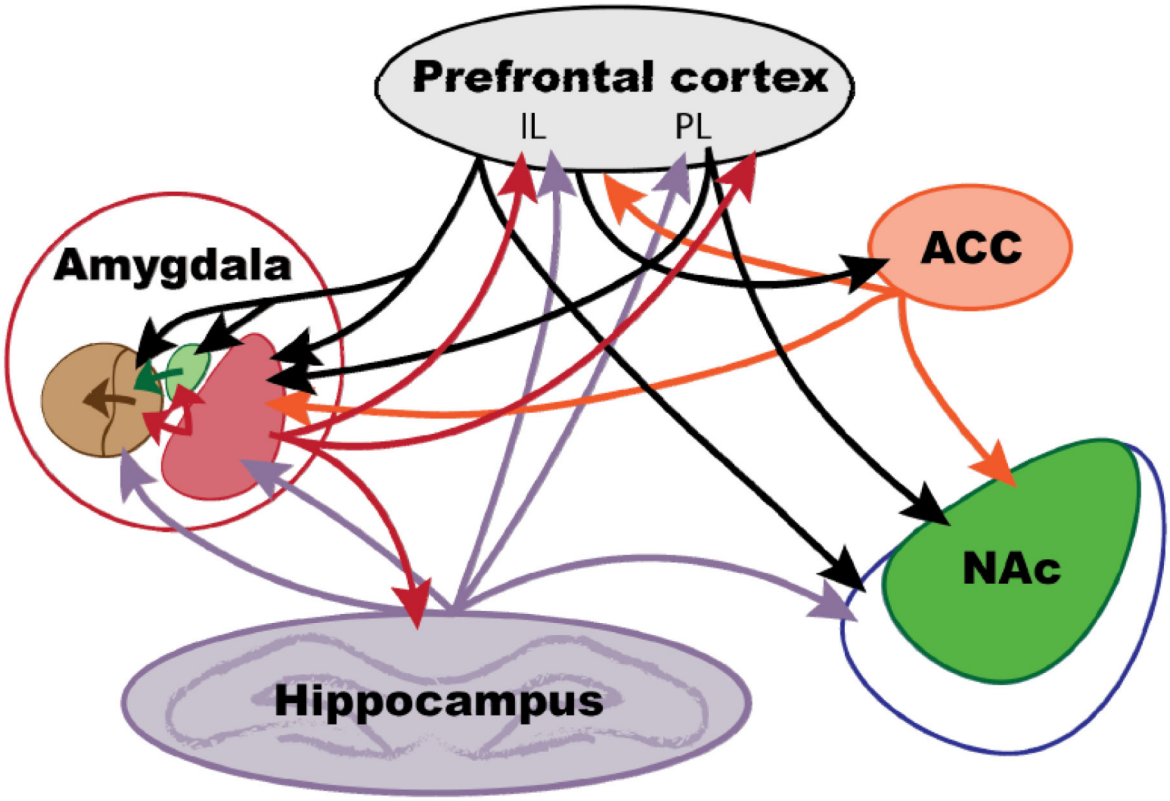

Figure 2. Pain-related cortico-limbic interactions.

Connections between cortical (prefrontal cortex including infralimbic, prelimbic, and anterior cingulate cortices) and limbic (amygdala, hippocampus, and nucleus accumbens) regions. Within the amygdala, the CeA (brown) with its medial (left) and lateral (right) divisions, ITC (green), and LA/BLA are shown. Within the nucleus accumbens, the core (green) and shell (blue) divisions are shown. mPFC, medial prefrontal cortex; IL, infralimbic mPFC; PL, prelimbic mPFC; ACC, anterior cingulate cortex; NAc, nucleus accumbens.