REVIEWS

Chronic Pain–Related Cognitive Deficits: Preclinical Insights into Molecular, Cellular, and Circuit Mechanisms

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Abstract

Cognitive impairment is a common comorbidity of chronic pain, significantly disrupting patients' quality of life. Despite this comorbidity being clinically recognized, the underlying neuropathological mechanisms remain unclear. Recent preclinical studies have focused on the fundamental mechanisms underlying the coexistence of chronic pain and cognitive decline. Pain chronification is accompanied by structural and functional changes in the neural substrate of cognition. Based on the developments in electrophysiology and optogenetics/chemogenetics, we summarized the relevant neural circuits involved in pain-induced cognitive impairment, as well as changes in connectivity and function in brain regions. We then present the cellular and molecular alternations related to pain-induced cognitive impairment in preclinical studies, mainly including modifications in neuronal excitability and structure, synaptic plasticity, glial cells and cytokines, neurotransmitters and other neurochemicals, and the gut-brain axis. Finally, we also discussed the potential treatment strategies and future research directions.

Introduction

Pain is a complex experience consisting of sensory, affective, and cognitive dimensions [1]. Chronic pain (CP) is often defined by pain duration, which persists beyond the healing process or lasts longer than 3 months [2]. Cognitive dysfunction is a particularly burdensome comorbidity of CP. Clinical evidence highlights that approximately 20% of CP individuals experience cognitive impairments [3], and those with multisite pain have a higher risk of dementia and faster cognitive decline [4]. Patients with CP are reported to experience impairments in memory, language, attention, processing speed, and visual-spatial function [5, 6]. Despite the comorbidity being clinically well-established, the involved neuropathological mechanisms are difficult to investigate in patients. The commonly used animal models of chronic pain, such as complete Freund adjuvant (CFA)-induced inflammatory pain, spared nerve injury (SNI)-induced neuropathic pain, and colitis-induced visceral pain, have contributed to exploring the neural mechanisms underlying CP-induced cognitive impairment and potential interventions [7].

One hypothesis for the comorbidity between chronic pain and cognitive impairment is that pain involves a complex neural network (called the "pain matrix"), which shares overlapping brain regions with cognitive function [8, 9]. Neuroimaging studies indicated that pain chronification is accompanied by reshuffling of brain activity from sensory to emotional and limbic structures [10]. Structural and functional plasticity changes in the corticolimbic regions contribute to the development of chronic pain, including the media prefrontal cortex (mPFC), anterior cingulate cortex (ACC), hippocampus, and amygdala [11]. Alternation in these regions during chronic pain may also disrupt cognitive processing. Here, we reviewed current preclinical

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research aimed at modeling comorbid cognitive deficits in chronic pain. We then discuss the possible mechanisms underlying CP-induced cognitive dysfunction in the relevant brain regions, involving neural circuits, neuronal changes, synaptic plasticity, glial cells, neurotransmitters, and other neurochemicals, as well as the gut-brain axis. Finally, we discuss the potential treatment strategies and future directions to enhance our understanding of the mechanisms underlying CP-induced cognitive deficits.

Pain and Cognitive Dysfunction

Chronic pain can disrupt normal cognitive processes, leading to impairments in learning and memory, attention, and cognitive flexibility [12]. We present an overview of preclinical evidence for CP-related cognitive impairment assessed by different cognitive domains (Table 1) and discuss the factors influencing these consequences. Our primary focus has been on discussing cognitive impairments in models of CP with a peripheral origin, specifically neuropathic pain, inflammatory pain, and visceral pain. Certain models, such as chronic unpredictable stress-induced pain and stroke-induced central pain, are excluded due to the challenge of establishing whether chronic pain is the primary cause of cognitive impairments.

Pain and Memory Impairment

Pain negatively impacts memory performance in rodents, including discriminative memory, working memory, and spatial memory, which highly relies on the normal function of the hippocampus and prefrontal cortex (PFC). Memory dysfunction usually occurs approximately 2 to 4 weeks after the injury and can last for at least a year.

Discriminative memory is often assessed by the novel object recognition test (NORT) in pain models. The interval between NORT training and testing phases, known as memory consolidation, allows evaluation of short-term (5 min to 2 h) and long-term (24 h) memory [48]. Our previous research has shown significant impairments in long-term recognition memory in a rodent neuropathic pain model [25, 26]. Interestingly, the results of short-term cognitive impairment in chronic pain are controversial. For instance, some studies noted short-term memory impairment in rodents with SNI lasting at least 1 month [17–21], while others observed no short-term memory impairment in partial sciatic nerve ligation (PSNL) and chronic constriction injury (CCI) models [14, 15, 49, 50]. It is worth noting that no memory dysfunction was evident within a week after pain surgery [13], suggesting that cognitive impairment might be associated with the progression of chronic pain over time. Additionally, the NORT has been used to assess discrimination between

dissimilar (recognition memory) and similar (pattern separation) objects in neuropathic pain mice. Guida et al. found that 1-month post-SNI mice struggled with both similar and dissimilar objects in short- and long-term memory tests, while 12-month post-SNI mice showed normal recognition of dissimilar objects but difficulty recognizing similar objects in long-term retention tests [22]. These results indicate that discriminative memory impairment in pain is relevant to pain progression, behavioral paradigms, and task difficulty.

Working memory (WM) is another form of short-term memory that involves planning and performing actions rather than passive information storage [51]. Y-maze is frequently used in preclinical studies to evaluate spatial working memory by measuring spontaneous alternations. Studies have indicated that the spontaneous alternations rate was decreased in the CCI and SNI groups within 2 to 3 weeks after surgery [15, 17, 23, 32, 52]. Other tasks, like food-reinforcement delayed spatial alternation in figure-eight [53] and T-mazes [54], revealed poor spatial working memory performance in mice with neuropathic and inflammatory pain.

Spatial reference memory involves the recall of spatial relationships between different locations or landmarks. The Morris Water Maze (MWM) task assesses long-term memory, with a probe trial conducted at least 24 h after training [48]. Xia et al. revealed that CCI mice initially displayed similar performance to controls in the MWM within 5 days, but exhibited increased escape latency and decreased time in the target quadrant after 21 days [34]. Furthermore, mice with chronic pain took longer to find the platform compared to those with acute pain or no pain, indicating spatial memory impairment during chronic pain [55]. Moreover, Mohammadi et al. demonstrated that inflammatory pain led to spatial memory impairment 7 days after CFA injection and gradually recovered by day 21 [31], which was correlated with the progression of thermal hyperalgesia. These results indicate that persistent painful stimulation is a primary contributor to cognitive pathology.

Pain and Attention Deficits

Clinical research has discovered that individuals with chronic pain often struggle with tasks requiring sustained attention [56]. Likewise, rats in the osteoarthritis group and SNI group exhibited higher error rates and more omissions in the 5-choice serial reaction time task (5-CSRTT) [38, 39]. Importantly, these impairments persisted even with temporary pain relief, suggesting permanent alterations in neurobiological attention mechanisms due to chronic pain [38]. Moazen and colleagues demonstrated that CCI rats exhibited attention deficits in the tasks of both low and high attention needs [40]. In addition, poor performance on visual attention tasks was found in both SNI mice [41] and colitis rats with chronic visceral pain [42].

Table 1 Summary of previous animal studies on pain-related cognitive impairments

Cognition modality	Pain model	Side	Species	Gender	Paradigm	Days	Key findings	Ref.
Short-term memory (discriminative memory)	SNI	/	Rat	M	NORT (10 min)	Day 4, 14	DI is decreased in SNI mice at day 14	[13]
	PSNL	L	Mouse	M	NORT (1 h)	Day 14	No impairment	[14]
	CCI	R	Mouse	M	NORT (1 h)	Day 28	No impairment	[15]
	SNL	R	Mouse	M	NORT (2 h)	Day 28	DI is decreased in SNL mice at day 28	[16]
	SNI	/	Mouse	M	NORT (2 h)	Days 14, 15, 30	DI is decreased in SNI mice	[17–20]
	CRPS	R	Mouse	M	NORT (2 h)	7 weeks	CRPS mice present reduced novel object exploration	[21]
	SNI	R	Mouse	M	NORT (1.5 h)	1 month	DI is decreased in SNI mice at 1 month	[22]
						12 months	No impairment	
Long-term memory (discriminative memory)	SNI	R	Mouse	M	NORT (24 h)	1 month	DI is decreased in SNI mice 1 month after injury	[22]
						12 months	SNI mice had difficulty recognizing two similar objects	
	PSNL	L	Mouse	M	NORT (24 h)	Days 7, 14, 28	DI is decreased in PSNL mice at days 14 and 28	[14]
	CCI	R	Mouse	M	NORT (24 h)	Days 14–28	CCI mice present reduced novel object exploration	[15, 23, 24]
	SNI	L	Mouse	M	NORT (24 h)	Days 14, 21	DI is decreased in SNI mice	[25–27]
	PSNL	L	Mouse	M	NORT (24 h)	6 months	DI is decreased in PSNL mice 6 months after injury	[28]
	CFA	R	Rat	M	NORT (24 h)	Day 16	CFA rats present reduced novel object exploration time	[29]
	Osteoarthritis	R	Mouse	/	NORT (24 h)	Day 30	DI is decreased in osteoarthritis mice	[30]
Short-term memory (spatial working memory)	CCI	R	Mouse	M	Y maze	Days 7, 14, 21, 28	Decrease in the spontaneous alternations rate at days 21 and 28 in CCI group	[15, 23]
	CCI	R	Mouse	M	Y maze	Days 7, 14, 21	Decrease in the spontaneous alternations rate at days 14 and 21 in CCI group	[31]
	SNI	/	Mouse	M	Y maze	Days 14, 28	Decrease in the spontaneous alternations rate in SNI group	[17, 32]
	SNI	L	Rat	M	Eight-arm maze	Days 11–20	SNI mice present lower average of correct alternations	[33]
	PSNL	L	Mouse	M	Y maze	6 months	Decrease in the spontaneous alternations rate in PSNL group	[28]

Table 1 (continued)

Cognition modality	Pain model	Side	Species	Gender	Paradigm	Days	Key findings	Ref.
Long-term memory (spatial reference)	CCI	/	Mouse	M	MWM	Days 5, 21	Increased escape latency and decreased time in the target zone at day 21 but not day 5 after surgery in CCI group	[34]
	CFA	R	Rat	M	MWM	Days 7, 21	CFA mice present increased mean latencies and decreased time in the target zone at day 7 but improved at day 21 after injection	[31]
	CCI/SNL	L	Rat	M	MWM	Days 21–28	CCI/SNL mice increased mean latencies and decreased time in the target zone	[35–37]
	SNI	/	Mouse	M	MWM	Days 15, 25–30	Increased mean latencies and decreased time in the target zone	[19, 32]
Attention	Osteoarthritis	L	Rat	M	5-CSRTT	Before and after CFA injection	More errors in accuracy and increased omissions in the task trials in the osteoarthritis group	[38]
	SNI	/	Rat	M	5-CSRTT	1 month	SNI mice present poor response speed, accuracy, and increased omissions in the task trials	[39]
	CCI	L	Rat	M	5-CSRTT	1 month	CCI mice present decreased choice accuracy, slower response, an increase in premature responses, and omissions in the task trials	[40]
	SNI	L	Rat	M	Visual attention task	6 months	Less exploration of the novel object in the SNI group	[41]
	Colitis	/	Rat	M	Visual attention test	Day 7	Less exploration of the novel object in the SNI group in colitic rats	[42]
Cognitive flexibility	Osteoarthritis	L	Rats	M	Gambling tasks	Days 5, 21, 56	Preference for the high-risk but less profitable choice in the osteoarthritis group	[43]
	SNI	L	Mouse	F/M	ASST	Day 21	Male (but not female) mice show a pain-related deficit in attentional set-shifting	[44, 45]
	SNL	L	Rat	M	The choice task	Day 21	Preference for familiar associations in SNL group	[46]
	Colitis	/	Rat	M	Gambling tasks	Days 7–10	Chronic viscera pain mice make less good decisions	[47]

SNI spared nerve injury, *CCI* chronic constriction injury, *CFA* complete Freund's adjuvant, *CRPS* complex regional pain syndrome, *PSNL* partial spinal nerve ligation, *SNL* spinal nerve ligation, *M* male, *F* female, *L* left, *R* right, *NORT* novel object recognition test, *MWM* Morris water maze test, *5-CSRTT* 5-choice serial reaction time task, *ASST* attentional set-shifting task

Pain and Cognitive Flexibility

Cognitive flexibility is an executive function primarily controlled by the PFC. Stephanie et al. used the attentional set-shifting task (ASST) to evaluate cognitive flexibility deficits induced by SNI. The results showed impairment in both male and female mice, with males requiring more trials and making more mistakes [44]. Importantly, short-term analgesia with clonidine did not reverse these deficits, indicating that chronic pain caused persistent deficits in high brain regions [44]. Furthermore, spinal nerve ligation (SNL) rats, osteoarthritis rats, and colitis rats exhibited a preference for the familiar but less profitable options in the gambling tasks [43, 46]. These findings highlight that chronic pain significantly disrupts executive functions.

Methodological Considerations

In considering methodologies for studying the mechanism underlying pain-induced cognitive impairment in preclinical research, several factors should be considered. Firstly, as mentioned above, the transition of pain from the acute phase to the chronic phase is crucial for memory impairment. Therefore, it is important to determine the time points of behavioral assessment. Secondly, task difficulty is a significant factor influencing cognitive assessment [57]. Phelps and colleagues found that rats with nerve damage showed memory deficits in more challenging tasks in the NORT, indicating that pain may consume cognitive resources, leaving limited capacity for complex tasks [58]. Furthermore, it is worth noting the potential impact of the side of pain on behavioral changes, due to the ascending pathways of nociceptive input and lateralization of brain function [59, 60]. For instance, Leite-Almeida et al. revealed that left-sided nerve lesions negatively affected emotional behavior

in SNI mice, while right-sided lesions worsened cognitive performance, especially in PFC-dependent tasks [60]. These differences may relate to different PFC activity changes in SNI-L (left) and SNI-R (right) rats [61]. Moreover, emerging evidence suggested sexual dimorphism in cognition, with male mice being more vulnerable to chronic pain-related cognitive deficits [44, 62]. Additionally, differences in animal species (mice vs. rats), chronic pain models, and baseline pain intensity can contribute to variations in behavioral outcomes. Therefore, a comprehensive understanding of the pain-cognition relationship in preclinical studies requires consideration and control of these methodological factors.

Neural Circuits Involved in Pain-Related Cognitive Dysfunction

Brain imaging studies showed that chronic pain engages the transformation of brain activity from the sensory areas to the corticolimbic regions. However, the continuous activation of corticolimbic circuitry may in turn induce their functional and anatomic alterations, and affect cognitive processes [63]. Here, we discuss the brain region and related neural circuits implicated in chronic pain-related cognitive dysfunction (Fig. 1).

Hippocampal-Related Circuits

The hippocampus is a key region of the limbic system involved in learning and memory, emotion, and sensory-motor integration. Neuroimaging studies revealed reduced hippocampal grey matter volume [64], altered shape [65], and disrupted functional connectivity in chronic pain patients [66]. Cognitive dysfunction in CP patients correlated with hippocampal structural and functional

Fig. 1 Altered neural circuits in the pain condition that contribute to cognitive deficits. (mPFC, media prefrontal cortex; PrL, prelimbic cortex; IL, infralimbic cortex; ACC, anterior cingulate cortex; Hip, hippocampus; dCA1, dorsal CA1; vCA1, ventral CA1; DG, dentate gyrus; VTA, ventral tegmental area; LHb, lateral habenula; BLA, basolateral amygdala; NAc, nucleus accumbens; MD, mediodorsal thalamus)
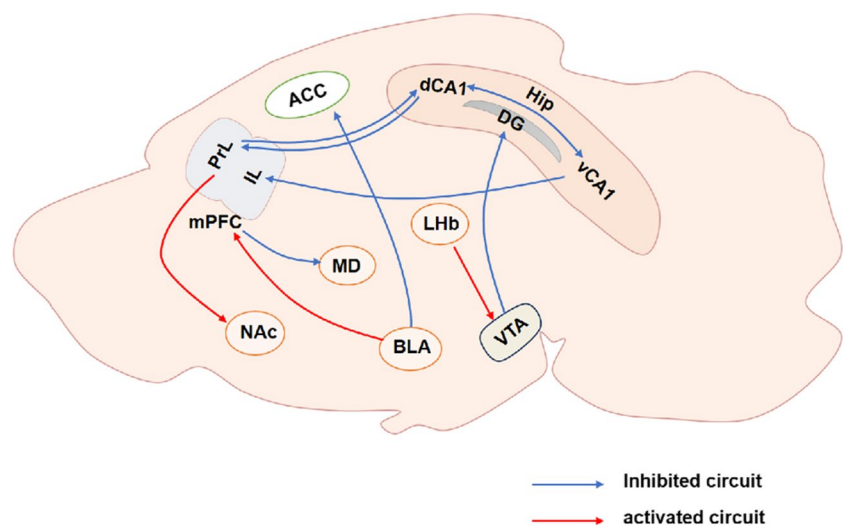
abnormalities [67], and those with persistent back pain exhibited a large decrease in hippocampal connectivity with mPFC [68].

Similar to clinical research, a recent study showed that SNI reduced the activity of hippocampal dCA1 neurons and dCA1-mPFC connectivity, and optogenetic activation of dCA1-mPFC projections reversed pain and memory deficits [69]. In the inflammatory pain models, the inhibited ventral hippocampus CA1 (vCA1)-infralimbic cortex (IL) pathway contributed to pain-related cognitive deficits [70]. Moreover, Cardoso-Cruz et al. found chronic neuropathic pain disrupted neuronal activity and theta oscillations across the dCA1-vCA1 axis during cognitive tasks, which was associated with changes in the dopaminergic balance of intrahippocampal networks [54, 71]. Hence, both the interconnectivity and extra circuitry of hippocampal subregions are disrupted by chronic pain. Neuroimaging reported a decrease in medial dorsal thalamus (MD) connectivity with mPFC and hippocampus in patients with CP, which correlates with negative emotions [72]. This leads us to speculate that MD, as an important relay of pain pathway, may be related to hippocampal dysfunction during chronic pain, although the specific mechanisms remain unknown.

mPFC-Related Circuits

The mPFC is a hub that integrates information about pain and cognition [73]. Structural and functional changes in the mPFC contribute to cognitive impairment in chronic pain. Brain imaging has shown a decreased mPFC grey matter volume in individuals with CP [64], which is closely correlated with working memory performance in patients [74]. In addition, functional MRI (fMRI) revealed that patients with chronic low back pain showed significantly less activation in the cingulate-frontal-parietal cognitive/attention network during attention-demanding tasks [75].

Animal research by Ji and colleagues demonstrated that the deactivation of the mPFC contributes to the cognitive comorbidity of pain. Chronic pain-induced hyperactivity in the basolateral amygdala (BLA) led to mPFC deactivation through glutamate-driven synaptic inhibition, causing decision-making deficits [76]. Similarly, Cardoso-Cruz et al. found that nerve lesions impaired spatial memory performance by disrupting information flowing and altering oscillation patterns in the mPFC–dCA1 circuit [53]. They further demonstrated that optogenetic inhibition of PL (prelimbic cortex)-mPFC glutamatergic neurons reversed neuropathic pain-induced WM deficits by restoring mPFC-dCA1 interaction [77] and local neuronal firing activity [78]. Furthermore, it is known that the mPFC-MD-hippocampus interactions

are involved in spatial memory [79], while chronic inflammatory pain reduced mPFC-MD activity during a spatial alternation WM task, leading to spatial working memory impairment [80]. In addition, chronic pain enhanced functional connectivity between PL-mPFC to NAc (nucleus accumbens), and its optogenetic inhibition restored pain-induced working memory deficits [81]. These results suggest that chronic pain disrupts the neural network connections of the mPFC and significantly impairs the cognitive process. Neuronal excitability changes [82] and neurotransmitter imbalances [83] may be the reasons for the mPFC inactivation.

ACC-Related Circuits

The ACC plays a critical role in pain perception, unpleasantness of pain, memory, and attention [84]. EEG and neuroimaging data showed activation of the ACC in both acute and chronic pain conditions [85, 86], which aligns with increased activity of pyramidal cells in the ACC in mice with neuropathic pain [87]. fMRI studies found that the activity evoked by pain and attention-demanding tasks is typically located in similar regions of the cingulate cortex, indicating that pain-induced ACC activity may influence cognitive process [88].

ACC receives nociceptive information from the thalamus and brain regions involved in the regulation of emotional states, such as the amygdala and insular cortex during pain [89]. It has been reported that the BLA and ACC form an interconnected neural circuit involved in decision-making [90]. Cao et al. found chronic visceral pain impaired theta oscillation synchronization between the BLA and ACC, contributing to execution deficits in visceral hypersensitivity (VH) rats [91]. Moreover, they found that reduced ACC L-lactate release suppressed neuronal theta synchrony, and optogenetic astrocytic activation restored BLA-ACC desynchronization and improved decision-making performance via lactate release in VH rats [47]. Furthermore, enhancing oligodendrocyte myelination restored ACC network function and improved cognitive behaviors in VH rats [92]. Importantly, it is essential to further investigate distinct ACC circuits that likely contribute to the development and maintenance of pain-induced cognitive dysfunction and their maladaptive changes during pain chronicity.

VTA-Related Circuits

The ventral tegmental area (VTA) is an important part of the mesolimbic dopamine (DA) system and participates in pain-related depression [93], anxiety [94], as well as reward and motivation [95]. Studies showed that reduced VTA-to-dentate gyrus (DG) dopamine projections negatively affected neurogenesis and spatial memory

formation during chronic pain [34]. The inhibited activity of VTA dopaminergic neurons caused by chronic pain may be regulated by lateral habenula (LHb). Alemi et al. demonstrated that LHb hyperactivity increased local GABAergic inhibition on VTA dopamine neurons, resulting in working memory impairment in CFA rats, which could be reversed by optogenetic inhibition of LHb [96]. It is worth noting that hyperactivity of LHb glutamatergic neurons induced endoplasmic reticulum stress, inflammatory responses, and dopaminergic neuronal damage in the VTA [97]. The disruption of VTA decreased dendritic spine density in the PFC and hippocampus and impaired cognitive function after surgery, which may be due to the decreased release of DA [97]. In summary, these limited findings highlight that dysfunctions of VTA and DA projections during pain have potential effects on cognitive aspects, and related molecular and cellular mechanisms need further investigation.

Cellular Mechanisms Involved in Pain-Related Cognitive Dysfunction

Chronic pain-induced cellular changes serve as the foundation for functional and structural alterations in brain regions and circuits. Alterations in neuronal plasticity and glial activation in the corticolimbic structures contribute to the cognitive deficits induced by chronic pain.

Neurons

Morphological and Electrophysiological Changes

The hippocampus and mPFC undergo significant morphological and functional changes in response to chronic pain (Table 2). Dendritic morphology, a key factor influencing grey matter volume in neuroimaging [101], is altered in neuropathic pain mice. This includes reduced dendritic

Table 2 A list of preclinical studies showing neuronal morphologic and functional changes in the chronic pain states

Pain model	Brain region	Neural morphologic and functional changes	Reference
CRPS (tibial fraction)	Amygdala	a. Increased complexity in dendritic structure b. Increased dendritic branching and length c. No change in average soma area and dendritic spine density	[21]
	Perirhinal cortex	a. Increased complexity in dendritic structure b. Increased dendritic branching and length c. No change in dendritic spine density	
	Hippocampus	a. No change in the number of neurons b. No obvious change in the dendritic spine density	
CCI	Hippocampus	**CA1 pyramidal neurons:** a. Decreased complexity of apical dendritic trees b. Decreased number of branches and length of the neurites c. Decreased dendritic spine density, mainly in the number of mushroom spines **CA3 pyramidal neuron:** a. Decreased in the number of branches and dendritic length b. Decreased dendritic spine, mainly in the number of mushroom spines **DG granule neurons** a. Increased complexity of basal dendritic trees b. Increased total number of branches and dendritic length c. Increased dendritic spine density, with decreased mushroom spines	[15, 23, 24, 52]
SNI	Hippocampus	**CA1 pyramidal neurons:** a. Decreased complexity of dendrites b. Decreased average number of junctions and total length of dendrites c. Decreased dendritic spine density d. Lower NMDA current	[50, 98]
SNI	mPFC	**Layer 2/3 pyramidal neurons:** a. Longer basal dendrites and increased dendritic branches of basal dendrites b. Increased spine density of basal dendrites c. Increased NMDA/AMPA current d. Increased excitability	[99, 100]
SNI	mPFC	**Layer 5 pyramidal neurons:** a. Less complexity and shorter apical dendrites b. Reduced glutamatergic currents c. Reduced membrane capacitance and increased input resistance d. Prelimbic layer 5 pyramidal neurons showed reduced excitability	[82, 100]

complexity, decreased spine density, and neuronal atrophy in CA1 and CA3 pyramidal neurons [15, 23, 98], along with decreased intrinsic excitability in CA1 pyramidal neurons of spared nerve injury (SNI) mice [69, 90]. In contrast, DG granule cells displayed an increase in the length, complexity of dendrites, and total spines' density, while mushroom spines that are responsible for the "storage of memories" were decreased [23]. These maladaptive changes in neurons are associated with decreased excitatory synaptic transmission, reduced BDNF levels, and neuroinflammation in the hippocampus induced by persistent pain [15, 50, 98].

Metz et al. observed changes in mPFC layer 2/3 (L2/3) pyramidal neurons after SNI, including increased basal dendrites complexity, spine density, NMDA/AMPK currents [99], and neuronal excitability [73, 100]. It has been found that chronic pain significantly increased noradrenergic innervation within the mPFC L2/3 neuron, which inhibited the HCN-mediated current and induced L2/3 pyramidal hyperactivity [102]. Conversely, layer 5 (L5) pyramidal neurons in the mPFC exhibited reduced complexity, shorter apical dendrites, and decreased neuronal excitability in neuropathic pain [100]. Shiers et al. reported shortened axon initial segments (AIS) in infralimbic (IL) layer 5/6 neurons in SNI mice, impacting neuronal excitability and presynaptic inputs [45]. The hypoactivity of L5 pyramidal neurons can be attributed to enhanced local GABAergic inhibition, reduced glutamatergic activation, and decreased cholinergic modulation during pain [82, 103–105]. Moreover, studies showed that the glutamatergic inputs from both the hippocampus and thalamus to mPFC L5 pyramidal neurons were weakened after SNI, which likely contributes to the mPFC deactivation in neuropathic pain and may impair PFC-dependent cognitive tasks [104]. Functional studies highlight the crucial role of PFC L5 pyramidal neurons in short-term memory [106]. Optogenetic activation of mPFC L5 pyramidal neurons can reverse object recognition memory deficits in Alzheimer's disease (AD) mice [106]. Similarly, optogenetic activation of the neural circuit from dCA1 to mPFC L5 pyramidal neurons alleviated neuropathic pain behaviors and improved novel object recognition ability in SNI mice [69]. Based on the layer-specific alterations in the mPFC induced by pain, further research can explore the role of different layers and

their outputs in pain and related comorbidities using layer-specific transgenic mice. In addition to pyramidal neurons, neuropathic pain increased spine density on mPFC interneurons, thus enhancing inhibitory inputs and suppressing glutamate signaling during working memory tasks [107]. These maladaptive changes induced by chronic pain collectively deactivate the mPFC and disrupt cognitive processes.

Synaptic Plasticity

Synaptic plasticity refers to the activity-dependent modification of synaptic strength [108]. Chronic pain significantly impacts synaptic plasticity in the hippocampus and can manifest as a reduction in synapses. Studies have found reduced expression of synaptic proteins in the hippocampus during chronic pain such as postsynaptic density protein 95 (PSD95), synapsin 1 (SYN1), vesicular glutamate transporters (vGLUTs), and Arc [24–26, 50], as well as decreased dendritic spine density in hippocampal pyramidal neurons, indicating a reduction in excitatory synapses [15, 20]. The resulting synaptic loss can disrupt information processing and transmission within neural networks associated with cognition. Moreover, chronic pain induced glutamatergic synaptic hypofunction, as evidenced by impaired excitatory postsynaptic currents (EPSCs) and reduced NMDA/AMPA currents in hippocampal pyramidal neurons [25, 98]. Long-term potentiation (LTP) and long-term depression (LTD) are forms of synaptic plasticity that have been widely studied in the context of learning and memory [25, 89]. As shown in Table 3, LTP at the lateral entorhinal cortex (LEC)-DG and CA3-CA1 synapses are diminished after high-frequency stimulation in neuropathic pain models, which may be disrupted by the impairment of excitatory synaptic transmission in hippocampal pyramidal neurons. However, no significant alteration was observed in LTD at hippocampal synapses under pain conditions [110].

In addition, Zhuo and colleagues have proposed that enhanced LTP and suppressed LTD of excitatory synaptic transmission in ACC result in a dysregulation of synaptic tone and hyperactivity in ACC neurons, which contributes to chronic pain and its related emotional changes [89, 112]. Behaviorally, postsynaptic-LTP at ACC synapses encodes

Table 3 Changes in various forms of hippocampal synaptic plasticity in the context of pain

Locus	Synapse between	Type of modulation	Key findings	Reference
Hippocampus	LEC-DG	LTP	LTP at LEC-DG synapses is impaired by chronic pain	[18, 19, 22, 32, 109]
	CA3-CA1	LTP	LTP at CA3-CA1 synapses is impaired by chronic pain	[25, 50, 52, 110, 111]
	CA3-CA1	LDP	Sham-treated and neuropathic mice are almost equivalent	[110]
	DG-CA3	PTP	PTP is decreased in the bilateral hippocampus	[64]

LTP long-term potentiation, *LDP* long-term depression, *PTP* post-tetanic potentiation

hyperalgesia and unpleasantness of pain, while presynaptic-LTP mediates pain-induced anxiety [89, 113]. Moreover, the restoration of ACC LTP and LTD has been shown to rescue peripheral pain hypersensitivity [113, 114]. Chronic pain is considered a result of plastic changes in the corticolimbic system, with synaptic plasticity as a common mechanism for pain and cognition [9]. Further investigation is needed to comprehend how changes in ACC LTP and LTD influence synaptic activity, neural circuit function, and their potential involvement in the cognitive impairment induced by chronic pain.

Intracellular and Extracellular Structural Changes

Both intracellular and extracellular structural alternations contribute to the maladaptive brain plasticity and cognitive deficits associated with pain. Microtubules (MTs) are essential structures for stable neuronal morphology and function, with the Tau protein, an MT-associated cytoskeletal element known to contribute to neuronal atrophy and dysfunction in neurodegenerative disorders, like AD [115]. Clinical evidence suggests that chronic pain increases the risk for dementia and AD [116]. In animal research, trigeminal neuralgia (TN) induced overexpression of phosphorylated tau protein and amyloid-β 1–42 in the cortex and hippocampus [117]. Guerreiro et al. first demonstrated that SNI triggered memory deficits and AD-related neuropathological changes, characterized by Tau hyperphosphorylation accumulation and neuronal atrophy in the hippocampus [118]. Genetic ablation and degradation of Tau effectively halted the hippocampal deficits induced by SNI, confirming the involvement of Tau in the memory decline associated with pain [118]. In addition, MT dynamic equilibrium also contributes to the memory decline in pain. You et al. found that SNI increased levels of stable microtubules in the hippocampus, and treatment of microtubule destabilizer improved hippocampal LTP and alleviated memory deficits in SNI rats [13].

The extracellular matrix (ECM) is a complex extracellular network that modulates neuronal plasticity and connectivity [119]. Chronic pain-induced changes in hippocampal neuronal structure, LTP, ECM microarchitecture, and ECM components and enzymes, such as increased levels of MMP8 [120]. Interestingly, normalizing these ECM imbalances reversed the memory decline, neuronal structure changes, and LTP disruption induced by chronic pain, which highlighted the involvement of extracellular mechanisms of pain-related brain plasticity [120].

Glial Cells

Increased inflammatory molecules, disruption of the brain-blood barrier (BBB), infiltration of immune cells, and glial activation are the hallmarks of neuroinflammation. These factors contribute to the establishment and persistence of central sensitization in pain [121].

Microglia

Microglia, as the innate immune cells in the CNS, are significantly increased and activated in supraspinal regions in the pain condition [27, 122]. Minocycline, a non-selective microglial inhibitor, alleviated pain-related cognitive dysfunction by inhibiting pro-inflammatory cytokine expression and oxidative stress and restoring synaptic plasticity in the hippocampus [98, 123]. High-mobility group box 1 (HMGB1) is a proinflammatory molecule involved in microglial activation and blockade of HMGB1 in the hippocampus effectively alleviated cognitive deficits induced by neuropathic pain [14]. Microglia can transform into either pro-inflammatory (M1) or neuroprotective (M2) phenotypes based on their activation mode. The hippocampus and mPFC exhibited increased M1-polarized microglia in the pain models that aggregated inflammatory response [49, 124]. Modulation of microglial polarization towards the M2 phenotype is beneficial for inhibiting neuroinflammation and improving behavioral outcomes [125]. Moreover, studies have reported that microglia-mediated excessive synaptic pruning contributed to synaptic loss and cognitive impairment in neurologic diseases [126]. Therefore, inhibition of microglia-mediated neuroinflammation is an essential target to improve behavioral abnormality following chronic pain.

Inflammatory cytokines and chemokines are released by activated glial cells, immune cells, and damaged neurons. Studies have shown the overexpression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6, in the hippocampus, PFC, and cerebrospinal fluid in pain models [55, 127–129]. These increased cytokines can also be detected in plasma samples from chronic pain patients [129]. Inhibiting TNF-α, IL-1β, and IL-6 or genetically downregulating their receptors could prevent microglia activation and maladaptive synaptic plasticity in the hippocampus and rescue cognitive impairment caused by pain [27, 33, 35].

Interestingly, certain studies have indicated that the presence of pro-inflammatory cytokines and reactive microgliosis appeared to be confined to the contralateral hippocampus of the injury side [130, 131]. However, accumulating evidence also suggested that chronic pain-induced neuroinflammation in the bilateral hippocampus and mPFC [98, 127]. It is worth noting that supraspinal neuroinflammation induced by pain originates not only from the CNS in situ but also from peripheral inflammation [132]. For example, chronic pain disrupted BBB permeability and increased leukocyte infiltration into the CNS [133]. Mai et al. found that the plasma chemokine CXCL12 mediated circulating monocyte

recruitment into the perivascular space, contributing to hippocampal neuroinflammation and cognitive impairment in the condition of neuropathic pain [134]. Given that nociceptive information is primarily conveyed to the contralateral hemisphere, neuroinflammation tends to be more robust in the brain regions contralateral to the injury site [135].

Astrocyte

Astrocytes serve critical functions in CNS homeostasis and neuronal metabolites [136]. Some studies reported reduced astrocyte numbers and atrophy in the hippocampus and mPFC, possibly due to the neurotoxic effects of noxious inputs [137–139]. Conversely, others found reactive astrocyte activation in these cognitive regions as a consequence of neuroinflammation [134, 140, 141]. These discrepancies may be related to the dynamic changes in astrocytes during different pain progression stages. Moreover, chronic pain induced alternations in the lactate metabolism of astrocytes, leading to disruptions in the supply of energy to the brain. Reduced lactate release from dysfunctional astrocytes decreased the excitability of dCA1 pyramidal neurons in SNI mice, leading to hippocampus-dependent memory deficits [69]. ACC astrogliosis in VH rats impaired L-lactate release under high activity demand conditions such as decision-making, which then suppressed ACC neuronal activity [47]. These studies enhance our understanding of astro-neuron interactions in brain regions during pain conditions. Future research should investigate astrocyte metabolic and functional changes and their interactions with other cells during comorbid pain and memory deficits.

Molecular Mechanisms of Pain-Related Cognitive Dysfunction

A multitude of molecules within the CNS play a role in the development of pain-induced cognitive deficits. In the following section, we provide a summary of current research on the role of these molecules in the comorbidity of pain and cognitive disorders, including neurotransmitters and their receptors, neuropeptides, neurotrophic factors, the endocannabinoid system, and the gut-brain axis.

Neurotransmitters and Their Receptors

Glutamate

As a major excitatory neurotransmitter in the CNS, glutamate plays an important role in the cognitive process. Glutamate acts on the postsynaptic ionotropic glutamate receptors, including N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

receptors (AMPARs), kainate, and metabotropic glutamate receptors (mGluRs) [142]. Dysfunction of glutamate and its receptors, NMDARs hypofunction in particular, is a key mechanism contributing to the cognitive deficits observed in chronic pain.

NMDA receptor is an important mediator of LTP and excitatory synaptic transmission [143]. In a previous study, we found reduced hippocampal glutamate concentrations and downregulation of NMDA receptor subunits NR1 and NR2B in SNI rats, along with disruption of hippocampal glutamatergic transmission and LTP [25]. The administration of d-serine, an endogenous NMDAR agonist, successfully restored hippocampal glutamatergic function and synaptic plasticity and alleviated cognitive decline induced by neuropathic pain [25]. Other studies also reported reduced hippocampal NMDARs and memory deficits in pain conditions [50, 144]. Furthermore, NMDA-mediated currents in CA1 pyramidal cells were attenuated, while AMPA function remained unchanged under neuropathic pain conditions [111]. These findings highlight the significance of NMDARs downregulation and hypofunction in the hippocampus in promoting cognitive impairment induced by CP. Moreover, reduced glutamate level in the mPFC is associated with emotional and cognitive dysregulation in chronic pain patients [145]. In SNI mice, Guida et al. found disrupted glutamatergic synapse homeostasis in the mPFC, including decreased extracellular glutamate levels and increased NR2B subunits [20]. They found that administration of NMDARs agonist d-Asp solution restored glutamate neurotransmission to physiological levels in the Mpfc and alleviated pain-induced cognitive deficits in mice [146].

LTP is triggered by Ca^{2+} influx through NMDARs but expressed by an increased abundance of AMPARs at the postsynapses [147]. It is widely accepted that upregulation of AMPARs-mediated LTP in ACC underlies the unpleasant experience of chronic pain [89, 148, 149]. However, decreased AMPAR subunits GluR1-3 were found in the hippocampus after PSNL, possibly due to increased AMPAR internalization and degradation in the neuroinflammatory context. This may be involved in the disruption of hippocampal synaptic plasticity [14, 144]. In the mature brain, most AMPARs consist of Ca^{2+}-impermeable GluR1/GluR2 subunits that maintain low cytoplasmic Ca^{2+}, while GluR2-lacking AMPARs are permeable to Ca^{2+} and dramatically alter synaptic function. Liu et al. found that neonatal repetitive noxious stimuli increased GluR2-lacking AMPARs in hippocampal neurons, which can result in elevated Ca^{2+} influx, dendritic spine dysfunction, and ultimately contribute to pain, spatial learning, and memory deficits in adulthood [150].

It also evidenced that negative modulation of mGluRs alleviates cognitive decline. mGluRs are widely distributed on the synaptic boutons that control excitatory

synaptic function by regulating glutamate release. Blockade of mGluR1 overcame cognitive deficits by attenuating local GABAergic inhibition and restoring the inactivation of mPFC neurons during pain [151]. Inhibition of mGluR5 ameliorated pain-related cognitive impairment and restored LTP disruption due to its correction of glutamate homeostasis [18]. Additionally, the mGluR7 negative modulator normalized increased mGluR7 expression in the hippocampus and cognitive deficits in SNI mice, which might be related to mGluR7's inhibitory effect on glutamate [17]. Therefore, these findings highlight the significance of proper functioning of the glutamatergic system for effective cognitive function.

GABA

GABA (γ-aminobutyric acid) serves as the primary inhibitory neurotransmitter in the CNS, acting on ionotropic $GABA_A$ and $GABA_C$ receptors, and metabotropic $GABA_B$ receptors. The GABAergic system is crucial for CNS function, particularly in learning and memory processes [152]. In chronic pain models, elevated GABA levels in the hippocampus [22, 32], and mPFC [153] contribute to an E/I imbalance, resulting in cognitive impairment. In the supraspinal region, GABA predominantly interacts with $GABA_A$ receptors to mediate rapid inhibitory synaptic transmission [154]. Blocking $GABA_A$ receptors in the mPFC can restore neuronal activity in the pain model, providing a potential strategy for ameliorating chronic pain-induced cognitive deficits [151]. Studies also linked memory impairment to enhanced tonic inhibition via $GABA_A$-α5 receptors [155, 156]. Cai et al. found a remarkable increase in the expression of the $GABA_A$-α5 receptors on the parvalbumin and somatostatin interneurons in the hippocampus in SNI rats, and antagonizing of these receptors improved cognitive impairment, highlighting the role of E/I neurotransmission imbalance in pain-induced cognitive dysfunction [157].

Monoamines

Monoamine neurotransmitters, including dopamine (DA), norepinephrine (NE), and serotonin (5-HT), are associated with pain and memory formation. Thus, it is imperative to discuss their roles in the comorbidity of chronic pain and cognitive decline.

The hippocampus and PFC mainly receive NE from the locus coeruleus (LC) [158]. The LC-NE system plays a significant role in arousal, cognition, pain processing, and stress response [159]. Chronic pain induces LC-NE dysfunction and increases the release of NE, contributing to pain facilitation and cognitive/emotional disorders [155, 156]. Peripheral nerve injury elevated NE concentration in the PFC and impaired cognitive function [40, 157]. Selective depletion

of norepinephrine in the LC alleviated attention deficits in chronic pain [40]. However, chronic pain-induced LC-NE system dysfunction is complex and likely based on downstream neuron function and location [116]. The decreased noradrenergic tone was found in the hippocampus in models of chronic pain [32, 109]. Microinjection of a β2 receptor agonist into dCA1 and activation of LC-dCA1 noradrenergic projections restored memory deficits in SNI mice, suggesting the role of the noradrenergic system in pain-induced cognitive dysfunction [160]. Stimulation of β-adrenoceptors with isoproterenol restored hippocampal LTP damage in chronic pain models [110]. Furthermore, studies demonstrated that NE can effectively alleviate neuroinflammation and microglial activation in neuropathic pain mice and AD mice [161–163]. Therefore, further research on the dysfunction of the LC-NE system in chronic pain, especially its targeted brain regions and cell types, may generate new ideas in the treatment of pain and related comorbidities.

Dopamine is a critical neurotransmitter in hippocampal-dependent memory processes [164]. Studies highlighted the significance of the hippocampal dopaminergic system in cognitive deficits associated with pain. Cardoso-Cruz et al. found that activation of dopamine D2/D3 receptors restored the impaired neural activity and dorsoventral connectivity in the hippocampus, ultimately improving working memory in SNI mice [71]. Conversely, blocking D2 receptors led to a significant decrease in theta-oscillation-mediated connectivity in the hippocampus and worsened spatial working memory deficits [54]. The dopamine released by the LC plays a crucial role in the dorsal hippocampus, influencing selective attention and spatial object recognition processes through D1/D5 receptors [165]. However, the effects of chronic pain on the dopaminergic system and its role in cognitive dysfunction are not fully understood.

5-HT plays a regulatory role in pain perception, cognition, and emotion [166]. Mice with chronic pain exhibited increased 5-HT levels in the hippocampus [55, 109], with potentially detrimental effects on hippocampal neurogenesis [167]. Jayarajan et al. reported that $5-HT_6$ receptor antagonists normalized neuropathic pain-induced memory deficits, possibly by attenuation of stress response in pain [168]. The widespread and diverse receptors underlie the complex function of 5-HT in the CNS. Subsequent research can focus on the potential role of 5-HT and its receptors in pain and cognitive processes.

Neuropeptides

Several studies have focused on the role of neuropeptides in cognitive processes. Our previous study found that the glucagon-like-peptide-1(GLP-1)/GLP-1 receptors axis was inhibited in the hippocampus of neuropathic pain mice [26], and its activation ameliorated chronic pain-induced

cognitive impairment by regulating hippocampal neuroinflammation and synaptic impairment [26, 140]. Orexin (Orx) is an excitatory peptide that contributes to arousal, appetite, and cognition. Pretreatment of Orx1 in the hippocampal effectively alleviated spatial memory impairment induced by orofacial pain [169], while blocking Orx1Rs in the BLA aggregated learning and memory dysfunction in migraine rats [170]. In addition, oxytocin (OXT), a classic hypothalamic neuropeptide for social memory and emotion, has been found to reduce hyperalgesia [171] and anxiety [172] induced by chronic pain. OXT treatment also alleviated cognitive impairments by decreasing hippocampal microglial activation and synaptic defects in a mouse model of sepsis-associated encephalopathy [173]. Collectively, neuropeptides show promise as effective treatments for chronic pain-induced cognitive deficits.

Neurotrophic Factors

Brain-derived neurotrophic factor (BDNF) is widely expressed in the CNS and plays an essential role in synaptic plasticity. In neuropathic pain mice, reduced BDNF levels in the hippocampus impaired synaptic plasticity [98]. Mature BDNF binds to the tropomyosin-receptor-kinase B (TrkB) receptor with high affinity, participating in mechanisms related to learning and memory, including LTP, neurogenesis, and synaptic efficiency and formation. In contrast, pro-BDNF exerts the opposing effect [172]. Enrichment environment mediated BDNF/TrkB signaling to ameliorate memory decline and enhance synaptic plasticity deficits in nerve-injured mice [24]. Peripheral inflammatory pain increased the microglia-dependent proBDNF/BDNF ratio, leading to hippocampal neuron death and spatial memory impairment in rats [31]. Furthermore, recent research demonstrated that the activation of BDNF release from the VTA to the DG improved memory decline in neuropathic pain mice via restoring hippocampal neurogenesis [34]. This study establishes a mechanistic link, relying on neural circuits and BDNF signaling to modulate neurogenesis, between chronic pain and cognitive deficits.

Endocannabinoid System

The endocannabinoid (eCB) system, consisting of cannabinoid receptors (CB1R and CB2R) and endogenous endocannabinoids (anandamide, AEA; 2-arachidonoyl glycerol, 2-AG), has been extensive studies in the field of pain, cognition, and emotion [174–176]. Palmitoylethanolamide (PEA), an eCB-like compound, alleviated neuropathic pain-related nociceptive, emotional, and cognitive behaviors by improving glutamatergic synapse homeostasis in the mPFC [20]. Additionally, PEA treatment restored impaired synaptic plasticity and neurogenesis in

the hippocampus of SNI mice [19]. Recent findings indicated that inhibition of AEA breakdown improved pain-related behaviors, enhanced LTP in the LEC-DG pathway, and normalized monoamine levels in the hippocampus via CB1 receptors following osteoarthritis [109]. These findings highlight the beneficial role of the endocannabinoid system in maintaining synaptic plasticity and homeostasis in the CNS during pain. Furthermore, both CB1R and CB2R agonists show potential in alleviating nociceptive and anxiety-like behaviors, whereas only CB1R agonists improved memory impairment in the osteoarthritis pain model [177]. These diverse effects may be attributed to the different distribution and cellular locations of the two cannabinoid receptors. In the condition of pain, CB1R is expressed throughout the CNS, with CB2R being less abundant in the brain [178]. The eCB system holds the potential to serve as a multi-target therapeutic approach for pain management.

Microbiota Gut-Brain Axis

The microbiota gut-brain axis has been demonstrated to play a significant role in pain modulation and cognitive dysfunction. It refers to bidirectional communication between the gut and the brain through immunological, neural, and hormonal signals, and the gut microbiota is now considered a key gastrointestinal factor [179]. Hua et al. found fecal microbiota transplantation (FMT) from the Sham group improved allodynia and cognitive performance in SNI mice by normalizing eCB signaling in the PFC, suggesting a link between gut microbiota, endocannabinoids, and neurological changes in chronic neuropathic pain (CNP) [180]. Gut dysbiosis in CNP may disrupt eCB signaling, exacerbating neuroinflammation and brain energy imbalances, ultimately resulting in cognitive dysfunction [180]. Evidence also highlighted the role of short-chain fatty acids (SCFAs) in cognitive function by regulating BBB permeability, immune response, and CNS maturation [181]. Studies found that chronic postsurgical pain (CPSP) mice with cognitive impairment had altered gut SCFAs-producing bacteria, and FMT from CPSP rats transmitted cognitive impairment. SCFAs supplement improved cognitive impairment in CPSP mice by enhancing histone acetylation and synaptic transmission [182]. Moreover, the gut-microbiota-brain axis via the subdiaphragmatic vagus nerve modulated neuroinflammation, and alleviated inflammatory pain and comorbid spatial working memory impairment in the CFA mice [183]. These results showed that gut microbiota dysbiosis might be an important etiology of cognitive impairment in chronic pain patients, and its neural mechanism needs further investigation.

Potential Intervention Strategies for Chronic Pain–Induced Cognitive Impairment

Effective pain analgesia and management may alleviate its associated cognitive impairment. Reports indicate that the chronic pain-induced gray matter decrease and cognitive network disruption can be partly recovered when chronic pain is treated successfully [68, 184]. However, the commonly used analgesic medications, such as gabapentin and opioids, have been shown to evoke or exacerbate existing cognitive impairment [185, 186]. The cognitive impairment induced by CP is marginally addressed in the clinic. Therefore, some potential treatments for cognitive impairment in CP patients are needed.

rTMS and tDCS

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are innovative tools in neurology and psychiatry for CNS diseases. They are able to modulate neuronal activities in stimulated areas, inducing functional changes in connected distant regions. It has been reported that rTMS stimulation on the dorsolateral prefrontal cortex (DLPFC) produced cognitive-enhancing effects in patients with depression, mild cognitive impairment, AD, and Parkinson's disease [187–190].

Low-frequency magnetic stimulation improved cognitive behavior by enhancing structural synaptic plasticity in the hippocampus of aging mice [191]. Additionally, tDCS on DLPFC enhances response speed and accuracy in cognitive tasks [192]. These findings suggest that rTMS and tDCS are potential treatments for cognitive impairment in chronic pain patients by targeting the prefrontal cortex and hippocampus, and modulating dysfunctional neural networks.

Anti-inflammation and Neuroprotection

Anti-inflammation and neuroprotection are key focuses in treating cognitive dysfunction induced by pain. Preclinical research indicated that anti-TNF-α, IL-1β, or IL-6 agents and their receptor antagonists may be effective treatments to reduce inflammation and exert neuroprotective effects [27, 33, 35]. Minocycline is widely used to inhibit microglia activation and has shown promising clinical applications in pain and cognition [193, 194]. Erythropoietin (EPO), as an immune modulator factor, improved recognition memory impairment through reducing hippocampal microglial expression, IL-1β production, hippocampal apoptosis, and necroptosis induced by inflammatory pain [195]. Metformin alleviated pain-related cognitive impairment and restored functional and morphological changes in the brain of neuropathic mice [44]. The neuropeptide GLP-1 receptor agonist

Fig.2 A schematic overview of alternations in neurochemical, neuroinflammatory, and neuroplastic mechanisms implicated in pain-related cognitive deficits
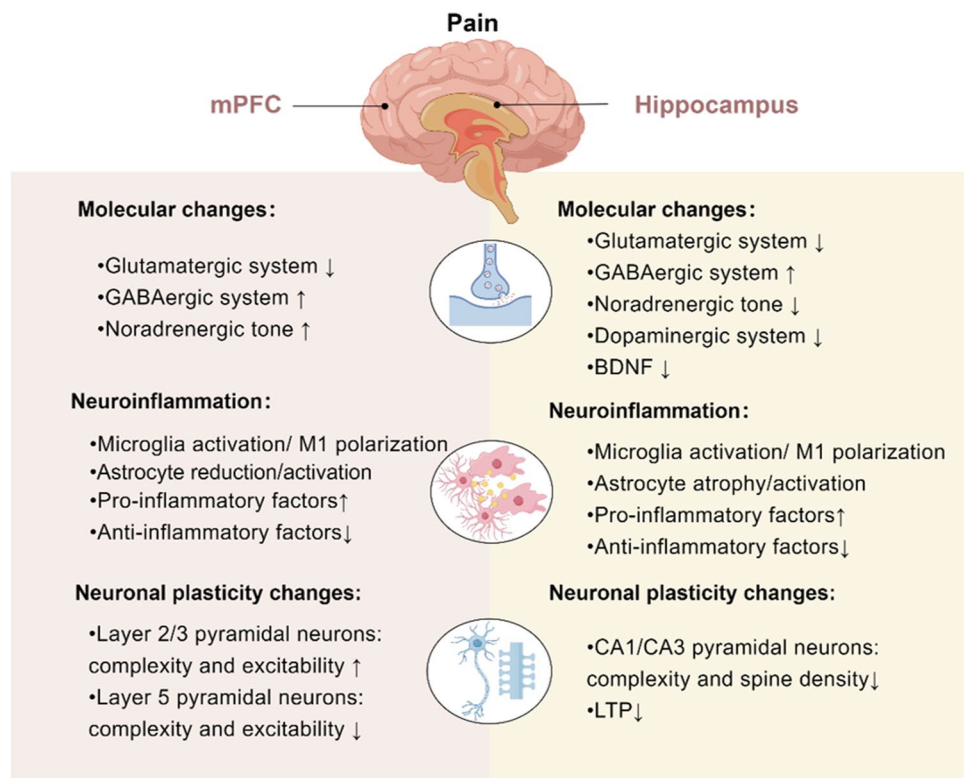
exendin-4 suppresses neuroinflammation, protecting neuronal plasticity in mice with neuropathic pain [26]. Moreover, treatments with NMDAR agonists d-serine and d-Asp can restore synaptic transmission and synaptic plasticity in the brain [25, 146, 196]. SCFA treatment improved gut microbiota, alleviated neuroinflammation and microglia activation in the cortex and hippocampus, and restored synaptic transmission in pain [182, 197]. Other targets, like BDNF, and eCB-like compound PAE, are potential treatments for cognitive impairments in CP patients. However, translating these preclinical findings into clinically useful medicines remains a challenge.

Conclusion and Future Directions

Clinical evidence has consistently demonstrated that patients suffering from chronic pain often experience cognitive impairments, which facilitates preclinical research to investigate the underlying mechanisms of CP-induced cognitive dysfunction. For this purpose, animal models seem necessary even though some findings from experimental animals may not be translated to bed-side. In this review, we have summarized methodological considerations for generating these models. Moreover, we proposed that chronic pain shares overlapping neuroanatomical substrates with cognitive processing, which may change the structure and function of these regions and lead to cognitive deficits. We discussed the mechanisms at molecular, cellular, and neural circuit levels that contribute to the comorbid cognitive deficits in chronic pain, primarily focusing on the hippocampus and mPFC (Fig. 2).

However, several important issues remain less studied. Firstly, the most currently used animal models of pain are chronic neuropathic and inflammatory pain, with less attention given to other prevalent types of clinical pain like chronic visceral pain, headaches, and musculoskeletal pain. Expanding investigations to include these different pain conditions can provide a more comprehensive understanding of the relationship between pain and cognitive deficits and accurately model the pain experiences in humans. Moreover, the current preclinical research on pain-induced cognitive dysfunction is largely restricted to the hippocampus and mPFC, with much less exploration of other relevant brain regions like ACC, amygdala, NAc, and LC. Despite extensive research on the ACC's role in pain and emotion disorders [84], there is still limited research on its direct mechanisms underlying pain-related memory impairments. Understanding local molecular and cellular changes in these brain regions and specific circuits by which pain disrupts cognitive processes is important in future research on pain-induced cognitive deficits, which

provides guidance for clinical drug targets and electro-physical therapies.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics Approval Not applicable

Consent to Participate Not applicable

Consent for Publication Not applicable

Conflict of Interest The authors declare no competing interests.

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