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From peripheral neurotoxicity to central dysfunction: linking neuropathic pain and cognition in chemotherapy-induced peripheral neuropathy

https://doi.org/10.1515/revneuro-2025-0146
Received December 19, 2025; accepted April 1, 2026;
published online April 21, 2026

Abstract: Chemotherapy-induced peripheral neurotoxicity (CIPN) represents a significant clinical burden, affecting 70–80 % of patients during treatment and persisting chronically in 20–30 % of survivors. While peripheral nerve injury is the primary pathological hallmark, emerging evidence demonstrates that central nervous system (CNS) dysregulation plays a crucial role in pain chronification and associated cognitive impairment. This review synthesizes recent findings on cortical and subcortical alterations that drive neuropathic pain processing in CIPN, examining dysregulated glutamatergic and GABAergic neurotransmission, altered voltage-gated ion channel expression, and central sensitization across key pain-modulatory brain regions including the prefrontal cortex, anterior cingulate cortex, somatosensory cortices, and periaqueductal gray. We address chemotherapy-induced cognitive impairment ("chemobrain") as a manifestation of shared neuroinflammatory mechanisms linking peripheral nerve injury to CNS pathology. In fact, peripheral neuropathy-triggered neuroinflammation, characterized by microglial activation and cytokine dysregulation, compromises the blood–brain barrier and impairs hippocampal-dependent memory, synaptic plasticity, and adult neurogenesis. The paper integrates findings from both animal models and human patients and discusses how animal models of CIPN reveal central nervous system engagement beyond peripheral pathology. This review emphasizes CIPN as a disorder profoundly affecting central pain modulation and cognition, requiring integrated therapeutic strategies addressing both peripheral and central nervous system pathology.

Keywords: chemotherapy-induced peripheral neuropathy; neuropathic pain; cognitive alterations; pain pathways; chemobrain

1 Introduction

According to the 2020 definition of the International Association for the Study of Pain (IASP), pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al. 2020). It is usually accepted that if pain persists beyond 3 months is considered chronic pain, a condition representing an important social, medical, and economic burden, with a prevalence estimated to be almost 20 % in the adult population worldwide (Mercer Lindsay et al. 2021). Moreover, chronic pain is often associated with depression, anxiety, and poor quality of life (Mullins et al. 2023).

It is well known that nociception is a complex process of encoding painful impulses, which are modulated at spinal and supraspinal level. In addition to its sensory component, the pain experience encompasses emotional–affective and cognitive dimensions, reflecting its complex and multifaceted nature.

Since the formulation of the gate control theory in 1965 by Melzack and Wall, a milestone in pain research, the role of the brain as an essential component in pain processing has been recognized. Numerous supraspinal regions are now known to be involved in various aspects of pain modulation. Among the most frequently implicated are the primary and secondary somatosensory cortices (S1, S2), prefrontal cortex (PFC), anterior cingulate cortex (ACC), insular cortex (IC), amygdala (AMG), thalamus, locus coeruleus (LC), and periaqueductal gray (PAG).

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The classification of pain identifies three main kinds of chronic pain: nociceptive, neuropathic, and nociplastic pain (Cao et al. 2024; Cohen et al. 2021). Nociceptive pain is the most frequent form of pain, caused by stimuli potentially leading to tissue damage. Neuropathic pain results from injury to the somatosensory nervous system. Nociplastic is a new term introduced in 2016 (Kosek et al. 2016), which defines pain arising from altered nociceptive function without clear evidence of tissue damage or involvement of the somatosensory system (Fitzcharles et al. 2021; Kosek et al. 2016).

This review deals with neuropathic pain due to peripheral nerve damage, and more specifically, to chemotherapy-induced peripheral neuropathy (CIPN). In CIPN, neuropathic pain is often accompanied by symptoms arising from central nervous system (CNS) dysfunction, particularly cognitive deficits and alterations in the emotional–affective domain. However, the mechanisms underlying this toxicity, which affects the nervous system at both peripheral and central levels, remain incompletely understood. A key point is whether the neurotoxic effects on the CNS result from a direct action of the chemotherapeutic agents, or whether alterations in pain-modulatory circuits – triggered by neurotoxic damage to peripheral nervous structures – may underlie the cognitive and emotional comorbidities.

In this paper, we summarize the nociceptive modulatory areas and pathways and recapitulate the most recent advances on central modulation of nociception in painful peripheral neuropathy, with a focus on CIPN animal models. A critical evaluation of recent studies investigating alterations in these brain regions in pain syndromes are provided, highlighting central sensitization, one of the most prominent reported changes, characterized by modifications in neurotransmission and in ion channel function.

Finally, association between neuropathic pain and cognitive dysfunction is frequently reported. Namely, among several proposed mechanisms underlying chemotherapy-induced cognitive impairment, often called “chemobrain,” neuroinflammation has been highlighted. Peripheral nerve damage could activate neuroinflammatory cascades where cytokine dysregulation triggers supraspinal dysfunctions. Here, we provide a detailed discussion of the various mechanisms proposed to link neuropathic pain and cognitive alterations.

2 Cortical and subcortical areas involved in nociception modulation

After the publication of the gate control theory for pain in 1965, Melzack elaborated the concept of the “Neuromatrix,” a wide neural network where pain experience would be not only the result of the somatosensory input itself but also of stress mechanisms, affective components, and genetic factors.

This extensive brain network would be characterized by specific genetically determined neural pathways and then modified by experience (Melzack 1999). In the original definition of Melzack, the concept of “Neuromatrix” was not pain specific, but rather it indicated a wide network generating patterns integrating nociceptive and non-nociceptive inputs.

Subsequently, “Pain Matrix” (Iannetti and Mouraux 2010) replaced the concept of “Neuromatrix” originally proposed by Melzack: it would represent a “pain specific matrix” constituted by a set of brain regions that consistently respond to nociceptive stimuli (Brooks and Tracey 2005; Ingvar 1999). Various authors have interpreted the degree of specificity of the “Pain Matrix” in different ways, for instance by focusing on distinct aspects or “subfunctions” of the pain experience. However, many researchers now criticize the use of the term “Pain Matrix,” as it implicitly suggests a dedicated pain-specific network, rather than the involvement of brain regions that are part of broader networks underlying the multidimensional aspects of pain (Mercer Lindsay et al. 2021). On the other hand, other researchers have maintained the term “Pain Matrix” to indicate the set of brain regions involved in pain perception and processing (Garcia-Larrea and Bastuji 2018; Legrain et al. 2011; Yao et al. 2023).

Here, the major brain areas with a role in pain transmission and modulation are discussed.

2.1 Primary and secondary somatosensory cortices (S1 and S2)

The S1 is the first destination of somatosensory information in the telencephalic regions. Regarding nociceptive input, the S1 gives an important contribution in discriminative aspects, localization and intensity evaluation of pain. Most of the S1 inputs come from the ventrobasal thalamus. In chronic pain, abnormal plasticity has been observed in the S1, with increased activity in cortical layers II and III and greater activation in downstream pain regions (Gamal-Eltrabily et al. 2021; Yao et al. 2023). The S2 receives and processes sensory inputs from the S1 and is also targeted by thalamic neurons. The S2 is an associative site for further integration of noxious stimuli with a possible modulatory role on nociception, even if a specific role in pain mechanisms has to be further clarified (Yao et al. 2023). Both S1 and S2 project to the posterior part of the IC (Labrakakis 2023). Chronic neuropathic pain conditions, including CIPN, are characterized by profound neuroplastic changes within S1 that are not limited to simple sensory processing

dysfunction. These adaptive changes involve multiple cellular and molecular mechanisms that contribute to pain chronification (Wrigley et al. 2009).

2.2 Prefrontal cortex (PFC)

Noxious stimuli activate the PFC, which is considered to have a critical role in integrating sensory and emotional–cognitive pain components. The PFC participates in pain modulation at cortical level, but it also has important connections with subcortical structures like the AMG and the PAG, through which it can have an antinociceptive function. Notably, the PFC receives significant projections from the medial thalamic nuclei, with the IC and other cortical areas representing some of the major connections (Gamal-Eltrabily et al. 2021).

In chronic pain, changes in the PFC structure and connections have been observed, in particular reduction of gray matter density, altered output from the PFC to the insula and the ACC, decreased activity of the PFC projections to the PAG, and reduced glutamate levels (Gamal-Eltrabily et al. 2021; Shiers and Price 2020).

In translational research, it must be noted that the rodent PFC considerably differs from the human PFC. In the human PFC, four main areas are commonly recognized: dorsolateral, dorsomedial, ventromedial, and orbital. The PFC medial regions are more related to pain processing and modulation. In mice and rats, there is not a conclusive consensus about terminology regarding the PFC subdivision. In fact, what is referred to as the prefrontal cortex largely corresponds to the medial prefrontal cortex (mPFC), which consists of the prelimbic and infralimbic cortex, the ACC with the CG1 and the CG2 areas, and the orbital area. The dorsolateral PFC is considered a specialization of primates, but its features could be almost in part found within the rodent mPFC. Regarding the ACC, its inclusion within the boundaries of the PFC varies among authors, depending on the criteria and species considered. Accordingly, it will be addressed in a dedicated paragraph. Another difference between species is that in rodents the whole PFC is agranular, while most of the human PFC is granular (Carlén 2017; Mercer Lindsay et al. 2021).

2.3 Anterior cingulate cortex (ACC)

The ACC, despite seemingly not being involved in processing pain intensity or location, is an important component in the pain perception network.

This cortex plays a role in many cognitive and emotional functions and shows increased neuronal activity and hyperexcitability during chronic pain experience. The ACC is related to the affective and emotional aspects of pain and has numerous connections with other regions involved in pain modulation, mainly mediodorsal (MD) thalamus, IC, AMG, and PAG (Gamal-Eltrabily et al. 2021).

Accordingly, it was shown that the ACC lesions can reduce the unpleasantness of pain perception but do not interfere with the sensorial discriminative feature (Juarez-Salinas et al. 2019).

In rodent models of chronic pain, cortical structural changes and increased neuronal activity mediated by upregulation of the mGluR1 (which inhibits hyperpolarization-activated cyclic nucleotide-regulated (HCN) channels) have been observed in ACC (Gamal-Eltrabily et al. 2021).

Functional magnetic resonance imaging (fMRI) studies in humans demonstrated activation of the ACC during experience of pain and also when observing others in situations of pain (Mercer Lindsay et al. 2021).

Some studies suggest that in chronic pain, circuitry dysfunction in the ACC would be more evident in women than in men (Yao et al. 2023).

2.4 Insular cortex (IC)

The IC is an important station of the spinothalamic tract and is implicated in nociception modulation and in the integration of different aspects of pain. As reported in fMRI studies on nociception, IC is a brain area constantly and early activated by pain stimuli. Moreover, the IC and the S2 are the only regions whose stimulation produces pain perception and insular lesions cause changes in pain sensitivity (Labrakakis 2023; Mercer Lindsay et al. 2021).

The anterior part of the insular cortex (aIC) is related to affective and emotional components, while the posterior part (pIC) mediates sensory aspects of pain inputs. The two parts have different connections and insular activation progress from the posterior to the anterior part (Frot et al. 2014).

The IC has extensive and often reciprocal connection with many other cortical and subcortical regions involved in pain processing. pIC is mainly connected with thalamic nuclei (ventroposterior lateral and posterior), S1 and S2, ACC, and midcingulate cortex (MCC), while the aIC is predominantly connected with medial thalamic nuclei, AMG, PFC, but also S1 and S2. Both insular regions receive information from the motor cortex, with the aIC being involved to a greater degree. The IC plays an important role in the modulation of nociception through outputs to the PAG, raphe

magnus nucleus, and locus coeruleus, all involved in the descending pain modulatory pathway. In chronic pain, functional and structural changes in the IC have been reported (Labrakakis 2023).

2.5 Amygdala (AMG)

Although the AMG is primarily considered a key structure for emotional and affective experiences, many studies recognize this nuclear complex as an important region also in pain processing and other kinds of salient stimuli. The AMG has widespread cortical and subcortical reciprocal connections. Among them, bidirectional projections with mPFC and orbital cortex, connections with hippocampus, nucleus accumbens, hypothalamus, medial thalamic nuclei, PAG, and other brainstem nuclei are worth to be mentioned. The AMG comprises numerous nuclei, which are differently grouped by various authors. The nuclear groups are often clustered in two regions, the central (CeA) and the basolateral (BLA) AMG (Meisner et al. 2022).

Both the CeA and the BLA nuclei are involved in pain modulation. The BLA, being the most recent part of the AMG, has major connections with cognitive cortical areas involved in processing information and driving behavior in pain experience. The CeA, a primarily GABAergic nucleus, represents the main AMG output, with important projections to the PAG. The CeA receives nociceptive inputs from parabrachial nucleus (PB), an important station in nociceptive pathways, and from the BLA (Mercer Lindsay et al. 2021; Neugebauer et al. 2020; Yao et al. 2023). A subset of GABAergic neurons within the CeA is activated by general anesthesia and exerts an inhibitory effect on pain (Mercer Lindsay et al. 2021).

Hyperactivity of the CeA has been related to neuropathic pain, but different kinds of neurons can contribute to both pro- and antinociception. In chronic pain, many different neuropeptides could be engaged to modulate the AMG output with an excitatory or inhibitory effect (Neugebauer et al. 2020).

2.6 Thalamus

The thalamus is a fundamental station for the transmission of pain information from the periphery to the cortex. It plays an essential role in the integration of ascending sensory inputs and constitutes a key component of the descending pain modulation pathways. The major portion of the spinothalamic neurons ends in the ventral posterior thalamic nuclei, whose neurons then project to S1 and S2; another conspicuous part of the spinothalamic neurons targets the intralaminar nuclei (ILN) and mediodorsal nucleus (MD), connected with the PFC and ACC and correlated with the emotional and motivational aspects of nociception (Mercer Lindsay et al. 2021). As previously mentioned, the thalamus also exhibits important connections with other key regions implicated in nociceptive processing, including the IC and AMG.

There is robust evidence of a role of the thalamus in the onset and persistence of neuropathic pain. In humans, the low-frequency oscillatory activity in the thalamocortical pathway, a basic and fundamental characteristic in the connection between thalamus and cortex, shows abnormal burst firing and distribution in chronic neuropathic pain (Pires et al. 2024; Yao et al. 2023). Moreover, resting state fMRI (rs-fMRI) showed decreased thalamocortical connectivity in painful polyneuropathies compared with painless polyneuropathies (Bismuth et al. 2025).

The importance of thalamus in pain processing is underlined by the thalamic pain syndrome, a centralized neuropathic pain disorder characterized by hypersensitivity and hyperalgesia, usually a consequence of a cerebrovascular accident involving thalamus. In the affected patients, thalamic pain onset could be acute, subacute, or delayed for many months from the stroke (Pires et al. 2024).

2.7 Periaqueductal gray (PAG)

The PAG is a midbrain area that integrates inputs from both cortical and subcortical regions to regulate stress responses, anxiety, autonomic control, pain processing, and other functions (Yao et al. 2023).

It receives and processes nociceptive information primarily deriving from PFC, ACC, AMG, hypothalamus, and also direct inputs from the spinomesencephalic tract and from PB, with important efferent connections toward brainstem regions, mainly the rostral ventromedial medulla (RVM) (Cao et al. 2024).

The importance of this region in the endogenous nociception modulation system has long been established. It is part of the descending pain modulatory system together with the RVM.

The PAG is composed of a heterogeneous cell population. Neurons containing endogenous opioids are more expressed in the ventrolateral PAG (vlPAG), which is the most deeply involved part in pain regulation. Indeed, its stimulation induces analgesia in humans by the release of endogenous opioids (Bagley and Ingram 2020). The projection from vlPAG to the RVM is recognized as the most important neural pathway in the descending pain modulation system.

2.8 Rostral ventromedial medulla (RVM)

The RVM is a brainstem region with a key role in nociception modulation through its descending output to the spinal dorsal horn (SDH), which can induce both facilitatory and inhibitory effects. The RVM receives projections from the thalamus, the PAG, and other brainstem areas and integrates inputs from higher cortical regions, which play a critical role in pain modulation (Cao et al. 2024; Yao et al. 2023).

The RVM represents the major target of the PAG projection in the descending pain modulatory pathway. The RVM exhibits a descending bimodal output, with its neuronal population distinctly divided into three types based on their responses to painful stimuli: ON cells, OFF cells, and neutral cells (Dogrul et al. 2025; Silva et al. 2013). ON and OFF cell activity results in enhanced or reduced nociception, respectively, but the role of neutral cells in pain modulation is not well defined. Neutral cells are serotoninergic, while most of the ON and OFF cells are GABAergic and exhibit different opioid receptors. An imbalance in the activity of ON and OFF cells was demonstrated in cases of neuropathic pain (Silva et al. 2013).

2.9 Locus coeruleus (LC)

The LC is a noradrenergic nucleus of the brainstem, located in the rostrolateral part of the pontine tegmentum near the fourth ventricle. It has widespread projections to the cerebral cortex and many other CNS regions. The LC neurons exhibit variable firing rates depending on behavioral state and arousal. They produce noradrenaline (NE), and notably, the LC is the sole source of NE to the cortex. The LC is thought to modulate several functions, including pain inhibition, attention, memory, as well as sleep and arousal (España et al. 2024).

As previously mentioned, the LC has widespread connections with several cortical areas relevant to pain processing, including the somatosensory cortex, PFC, insula, ACC, and AMG, and is also involved in the emotional component of pain. Additionally, in the descending inhibitory pathway, the PAG and RVM are interconnected with the LC, which exerts an important modulatory role in chronic pain (Bagley and Ingram 2020; España et al. 2024; Su et al. 2025).

LC provides major noradrenergic projections to the spinal dorsal horn, and activation of this pathway has been reported to alleviate neuropathic pain (Li et al. 2022b).

3 Neural network in pain processing

In pain conduction, processing, and modulation, ascending and descending pathways work together for the integration of sensory and emotional aspects. All the cortical and subcortical areas described in the previous paragraph are somehow involved in these circuits (see Figure 1).

Pain sensations originate at nociceptor level and are transmitted through afferent fibers to the spinal cord and brainstem, where spinothalamic and trigeminothalamic tracts are formed. These are the most important pathways for pain conduction at supraspinal level. From the spinal cord, the sensory component is conveyed to the thalamus and then to S1 and S2, an IC for the discrimination of pain features and localization. Other important pathways are spinomesencephalic, spinoreticular, and spinohypothalamic tracts. The affective–emotional and cognitive aspects of nociception are transmitted from the spinal cord to the PB, an important station at the junction of the pons and midbrain, to AMG, and then to ACC and PFC, in particular mPFC (Cao et al. 2024). Some authors denominate these two neural tracts, respectively, the lateral and medial ascending pathways for pain (Yao et al. 2023).

The supraspinal pain network features a descending pain modulatory circuit passing through the midbrain, comprising PAG and its downstream target RVM. PAG is one of the subcortical regions playing a major role, and in particular, vlPAG exerts its function through projections to RVM that in turn transmits to interneurons in the dorsal horn (Yao et al. 2023). Another brainstem area receiving inputs from PAG that plays an important role in pain modulation is the LC (Mercer Lindsay et al. 2021).

The descending pathway for pain modulation receives inputs from different brain regions that influence brainstem structures in order to carry out an antinociceptive function.

Changes in connections and cortical remodeling, which could underlie pain modulation alterations, have been reported in several brain regions involved in the onset and maintenance of chronic pain (Yao et al. 2023). Reduced activity of ACC and PFC (Gamal-Eltrabily et al. 2021) and variable changes in IC, PFC, and other brain areas have been observed (Labrakakis 2023; Shiers and Price 2020; Yao et al. 2023). The S1 cortex demonstrates abnormal cortical reorganization following peripheral nerve injury (for instance after limb amputation), with studies showing that the degree of somatotopic reorganization directly correlates with pain intensity in neuropathic conditions. In subjects with spinal

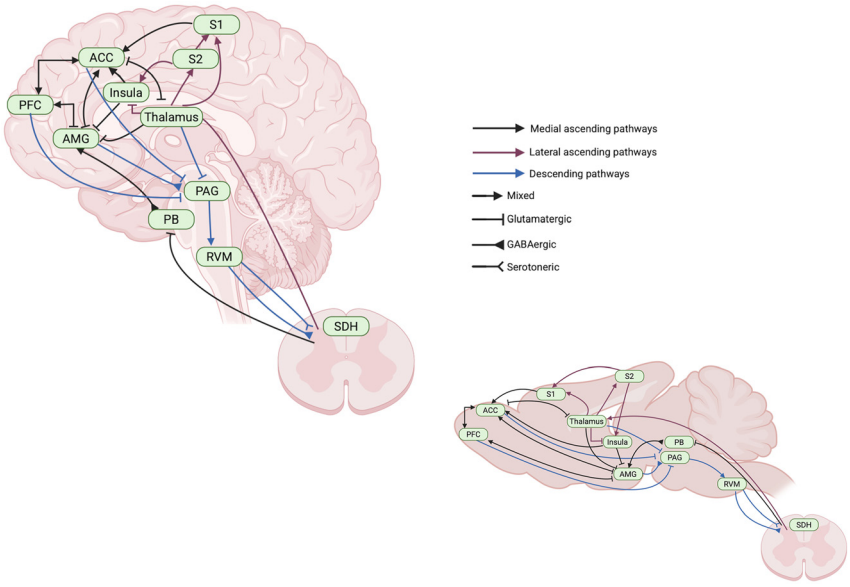

Figure 1: Representative image of neural networks involved in pain processing in human (A) and rat (B) CNS. Ascending and descending pathways, with respective neurotransmitters, are shown according to the arrow styles. ACC: anterior cingulate cortex; AMG: amygdala; PAG: periaqueductal gray; PB: parabrachial nucleus; PFC: prefrontal cortex; S1: primary somatosensory cortex; S2: secondary somatosensory cortex; SDH: spinal dorsal horn; RVM: rostral ventromedial medulla.

cord injury, a reorganization characterized as a medial shift of digit representations toward cortical normally representing denervated body areas has been reported, effectively creating a "cortical phantom" that may contribute to ongoing pain perception (Li et al. 2022a; Wrigley et al. 2009). Another study demonstrated that spontaneous chronic pain involves distinct brain mechanisms from acute pain. Indeed, sustained high spontaneous pain in chronic back pain patients specifically activates the mPFC (including rostral anterior cingulate), while increasing pain states activate the IC (Baliki et al. 2006).

The different areas related to the descending pathways participate in the constitution of facilitatory and inhibitory systems, with a certain degree of overlap, involving different kinds of neurons. In physiological conditions, these systems act together to maintain a balance. This equilibrium may be altered in pain hypersensitivity conditions, which lead to a decreased activity of the inhibitory pathways favoring an enhanced role of the facilitatory systems, not particularly active in normal conditions. This alteration represents a critical situation for the development of neuropathic chronic pain (Cao et al. 2024).

Some studies reported a relationship between chronic pain perception and default mode network (DMN), a group of separate, but functionally connected, brain areas mostly located in the medial part of the hemispheres (mPFC, posterior cingulate cortex, precuneus, inferior parietal lobule, and others). Changes in DMN connectivity have been correlated with pain intensity and resilience as well as mood (Cao et al. 2024; Hemington et al. 2018) in chronic pain syndromes.

Overall, chronic pain is associated with enhanced activity within brain regions implicated in emotional and motivational processing, including the mPFC, AMG, ACC, and others. Evidence suggests that during the transition from acute to chronic pain, brain activity progressively shifts from predominantly sensory networks toward mesolimbic circuits involved in affective and motivational regulation. These cortical adaptations may contribute to the persistence of pain. In this framework, neuroplastic remodeling of brain networks may represent a key mechanism underlying the long-term maintenance of chronic pain (Medrano-Escalada et al. 2022).

4 Neuropathic pain in peripheral neuropathy: focus on CIPN

Neuropathic pain is one of the most psychologically and physically disabling kinds of pain (Cao et al. 2024; Cohen et al. 2021), and it is defined by the IASP as "Pain caused by a lesion or disease of the somatosensory nervous system." Neuropathic pain may be caused by different disorders of the central and peripheral nervous system and is often a major feature in peripheral neuropathies. A classification of chronic neuropathic pain has been provided by the IASP for the 11th revision of the "International Statistical Classification of Diseases and Related Health Problems" (ICD-11) (Scholz et al. 2019). This classification has been implemented with a distinct category called chronic cancer–related pain, which embraces many diagnostic entities including chronic painful CIPN.

Patients affected by peripheral neuropathy with neuropathic pain share common symptoms and signs, regardless of the underlying cause. They complain of continuous or intermittent spontaneous pain often described as shooting, burning, electrical-like, that could also be evoked by touch or

cold. Typically, an increased response to painful stimuli (hyperalgesia) or a painful response to innocuous stimuli (allodynia) may be observed. Beyond pain, sensory impairment is often part of the clinical picture, such as sensory loss or reduced sensation variably involving all sensory modalities (hypesthesia), or abnormal sensations like paresthesia and dysesthesia (tingling, pricking, and numbness). The coexistence of positive symptoms together with reduced sensitivity is typical of painful peripheral neuropathies. In a lower number of patients also motor and autonomic dysfunctions may occur (Cohen et al. 2021; Finnerup et al. 2021; Scholz et al. 2019). Besides neurological examination, nerve conduction studies (NCS) constitute a basic diagnostic tool in peripheral neuropathies, while quantitative sensory testing may be useful but not necessary. If small fibers involvement is suspected, a skin biopsy to measure intraepidermal nerve fibers density could be indicated (D'Souza et al. 2023).

From the pathophysiological point of view, in peripheral neuropathic pain injured fibers, particularly C and Aδ fibers develop ectopic activity with increased excitability in pain pathways. Enhanced expression of voltage-gated sodium channels (VGSCs) and other changes in calcium and potassium channels contribute to spontaneous and ectopic discharge and to an increase in excitability states (Dib-Hajj et al. 2015). In addition, nerve damage is accompanied by local inflammation, which contributes to progression of axonal damage (Liu et al. 2019). Inflammatory response triggers sensitization, with threshold reduction and increased response to painful stimuli. Due to the persistence of nociceptive stimuli after peripheral nerve injury, sensitization also involves nociception-related spinal and supraspinal areas. Activation of astrocytes contributes to neuronal hyperexcitability and neuropathic pain maintenance by releasing proinflammatory cytokines, recruiting NMDA receptor subunits to synapses and altering sphingolipid metabolism, as shown in the spinal cord (Li et al. 2026; Singh et al. 2024; Xie et al. 2024). Moreover, structural plasticity leading to incorrect peripheral reinnervation with dysfunction of collateral sprouting and nociceptors together with central hyperexcitability have been reported. All these changes in peripheral and central nervous systems contribute to maintaining chronic neuropathic pain (Gangadharan et al. 2022; Rosenberger et al. 2020).

Among the different types of peripheral neuropathies characterized by neuropathic pain, we specifically address CIPN, a common and frequently unavoidable adverse effect of many antineoplastic drugs. CIPN onset occurs during antineoplastic treatment in 70–80 % of patients, commonly after a few cycles of chemotherapy and may persist as a chronic form in almost 20–30 % of them (Sałat 2020; Was et al. 2022). CIPN, in most cases, is a length-dependent polyneuropathy, with the typical distal and symmetric distribution of the symptoms outlined above.

CIPN may be accompanied by CNS symptoms, such as mood disorders (anxiety, depression) and cognitive impairment. In a population of long-term colorectal cancer (CRC) survivors treated with chemotherapy, higher grade of CIPN was to a greater extent associated with mood disorders (anxiety and depression), and these subjects also reported more fatigue (Bonhof et al. 2019). Cognitive alterations associated with anticancer treatment are generally referred to as "chemo-fog" or "chemobrain," meaning chemotherapy-induced cognitive impairment (CICI). Cognitive changes may affect up to 75 % of chemotherapy-treated patients and may persist for some years following the end of treatment in a considerable percentage of survivors (Alhowail and Aldubayan 2021; Mayo et al. 2021). Difficulty in concentration, attention and learning, memory loss, and impaired executive functions are some of the symptoms ascribed to "chemo-fog," often accompanied by mood disorders. Onset, duration, and extent of cognitive dysfunction are variable (Dias-Carvalho et al. 2022; Mayo et al. 2021; Was et al. 2022). These CNS symptoms together with chronic neuropathic pain due to peripheral nerve damage could severely impair daily life activity.

The main classes of chemotherapeutic agents causing a peripheral neurotoxicity that often results in neuropathic pain are platinum drugs, antitubulins, proteasome inhibitors, and certain immunomodulatory drugs such as thalidomide. The development and clinical picture of neuropathy depend on the chemotherapeutic drug employed. Although these agents can all be responsible for the onset of neuropathic pain, the overall clinical features are remarkably different.

Some antitumor agents, such as oxaliplatin, paclitaxel, and docetaxel, also cause an acute and transitory form of painful syndrome ensuing during or immediately after drug administration (Cavaletti and Marmiroli 2020; Tamburin et al. 2019). The symptoms of oxaliplatin acute neurotoxicity (painful paresthesias associated with cramps and muscular spasms) typically occur within hours after the drug infusion, are evoked by cold exposure, and last 48–72 h before complete recovery. These symptoms recur at least in 80–90 % of oxaliplatin-treated patients at any treatment cycle with the same features (Cavaletti and Marmiroli 2020; Marmiroli et al. 2017a). Paclitaxel, more than docetaxel, causes in most treated patients (70–80 %) the so-called "taxane-induced acute pain syndrome," which generally shows a peak at the third/fourth day after the treatment. It is characterized by diffuse myalgia/arthralgia, but pain is also localized in hands and feet, usually remitting in a few days (Marmiroli et al. 2017b; Tamburin et al. 2019; Velasco-González and Coffeen 2022).

Beyond the above described acute painful syndromes, patients treated with oxaliplatin or taxane frequently develop a chronic sensory and sensory-motor peripheral neuropathy,

respectively, where neuropathic pain is more likely to be reported in taxane-treated patients than in oxaliplatin-treated patients (Cavaletti and Marmiroli 2020; Marmiroli et al. 2017b; Velasco-Gonzales and Coffeen 2022).

The proteasome inhibitor bortezomib can induce the most severe chronic neuropathic pain.

Bortezomib-induced painful neuropathy can ensue in a variable percentage of patients during the treatment, and typically pain is paralleled by the onset of distal symmetric sensory impairment (Argyriou et al. 2014); once ensued, painful sensation often increases in severity until causing treatment reduction or withdrawal (Li et al. 2020b).

Vinca alkaloids (mainly vincristine) and thalidomide can induce a sensory-motor neuropathy characterized by autonomic impairment and a sensory neuropathy, respectively, but in both cases, pain onset is not a prominent feature, being reported only in few patients (Marmiroli et al. 2017b).

Table 1 shows the main antineoplastic drugs inducing peripheral neurotoxicity, their anticancer action, and their clinical use.

Table 1: The most commonly used neurotoxic chemotherapy agents with their main employment, mechanism of cytotoxicity, and neurotoxic profile.

Drug	Mechanisms of anticancer action	Main employment	Peripheral neurotoxicity
Platinum drugs			
Cisplatin (Albers et al. 2014; Burgess et al. 2021; Santos et al. 2020)	DNA crosslinks	Advanced ovarian, testicular, head and neck, non–small-cell lung (NSCL) cancers.	Incidence: up to 90 %. Symptoms: paresthesia (tingling, burning, prickling), numbness (loss of sensation), pain (stabbing, burning, or electric shocks), clumsiness of fine movements, decreased vibratory sensation and loss of proprioception, gait instability, "Coasting."
Carboplatin (Albers et al. 2014; Burgess et al. 2021)	DNA crosslinks	Ovarian cancer.	Incidence: 4–15 %. Symptoms: Mild pain, paresthesias, tingling, and numbness, usually in the hands and feet, eventually gait ataxia.
Oxaliplatin (Albers et al. 2014; Burgess et al. 2021; Kang et al. 2021)	DNA crosslinks	Advanced or recurrent colon cancer, adjuvant in colon cancer, stomach.	Acute, transient syndrome: Incidence: 85–95 %. Symptoms: Reversible symptoms consisting of paresthesias, cold hypersensitivity, jaw and eye pain, ptosis, leg cramps, and visual and voice changes. Chronic syndrome: Incidence: 50–70 %. Symptoms: Paresthesias in the feet and numbness of toes and fingers, impaired proprioception, ataxia, clumsiness of fine movements, and gait disturbances. Decreased vibratory sensation and loss of proprioception.
Antitubulins			
Taxanes (paclitaxel, docetaxel) (Burgess et al. 2021; Staff et al. 2020)	Tubulin binding (microtubules assembly)	Ovarian, breast, non–small-cell lung cancer (NSCL), gastric, pancreas, prostate, head and neck cancers, melanoma, Kaposi's sarcoma.	Incidence: 50–90 %. Symptoms: Paresthesia, numbness in the hands and feet, neuropathic pain. Occasional deficits in motor functions. Docetaxel exhibits same, but milder, symptoms.
Vinca alkaloids (vincristine, vinblastine) (Li et al. 2020a; Burgess et al. 2021)	Tubulin binding (microtubules disassembly)	Acute leukemia, Hodgkin and non-Hodgkin lymphoma, neuroblastoma.	Incidence: 30–40 %. Symptoms: Loss of ankle reflexes, areflexia, paresthesias, mild sensory loss, mild impairment of vibration, weakness, motor impairment. Vinblastin exhibits no or mild neurotoxicity.
Epothilones (Brogdon et al. 2014)	Tubulin binding (microtubules assembly)	Breast and multidrug-resistant solid tumors.	Incidence: 40–80 %. Symptoms: similar to taxanes.
Proteasome inhibitors			
Bortezomib (Burgess et al. 2021; Sogbein et al. 2024)	Inhibition of proteasome activity	Multiple myeloma, mantle cell lymphoma.	Incidence: 50 %. Symptoms: Severe neuropathic pain and burning sensation, sensory ataxia autonomic neuropathy, including upright hypotension.

Effective prevention and/or treatment for neuropathic pain and other symptoms of CIPN are still very limited. To date, the only therapy recommended by ASCO guidelines for CIPN is duloxetine, a serotonin and norepinephrine (SNRI) reuptake inhibitor (Jordan et al. 2020; Loprinzi et al. 2020).

Some studies concerning neuropathic pain demonstrated that resistance to treatment is higher in CIPN than in other types of neurological diseases (Sałat 2020).

Despite there is no rationale-based evidence for their efficacy, several pharmacological and nonpharmacological treatments for chronic pain in CIPN have been proposed.

The use of tricyclic antidepressants is reported but not supported by literature data, and the utility of gabapentinoids and oral opioids for the treatment of painful CIPN remains uncertain. Clinical trials employing one or more topical substances (menthol, amitriptyline, ketamine, capsaicin, and others) reported contrasting results on pain symptoms, with capsaicin giving the best results (D'Souza et al. 2023).

Regarding nonpharmacological therapies, physical treatment, acupuncture, transcutaneous electric nerve stimulation (TENS), and scrambler therapy have been employed for the treatment of painful CIPN (Avallone et al. 2022; D'Souza et al. 2023). Reported improvements in painful CIPN with physical therapy, acupuncture, and TENS treatment are often inconsistent and/or not statistically significant. In randomized controlled trials investigating scrambler therapy, only small or no improvement in pain symptoms have been observed. Overall, these kinds of nonpharmacological treatments need to be further investigated in future ad-hoc studies (Cao et al. 2024; D'Souza et al. 2023).

With regard to the role of neuromodulation interventions, in selected CIPN patients with severe and persistent pain, spinal cord, dorsal root ganglia (DRG), or peripheral nerve stimulation have been performed. However, methodological differences among studies and the low number of patients recruited make it necessary in the future to perform prospective studies with an adequate number of patients (D'Souza et al. 2022; Gupta et al. 2024; Vu et al. 2024).

5 Animal models of neuropathic pain in CIPN

To investigate the mechanisms of CIPN and find new treatments, researchers can use cellular (*in vitro*) and animal (*in vivo*) models. *In vitro* studies are valuable for exploring specific cellular processes, but they cannot fully capture the complexity of an entire organ system. Because of this, results from *in vitro* studies need to be verified in living organisms. Animal models, while overcoming many limitations of *in vitro* studies, present their own challenges. They are resource-intensive, time-consuming, require specialized training, and must adhere to strict ethical guidelines (Bruna et al. 2020). To ensure research findings are relevant to patient care, preclinical studies should prioritize outcome measures and biomarkers that have already demonstrated a clinical significance (Cavaletti 2014).

Most animal models for CIPN involve injecting chemotherapeutic drugs. While intraperitoneal (i.p.) injections are common in research, they are not used in patients due to local toxic effects. Intravenous (i.v.) injections in animal models more closely mimic the human clinical situation.

Assessing pain and discomfort in rodents can be challenging. Since evaluating spontaneous pain and tingling is difficult, researchers frequently use techniques able to measure mechanical hypersensitivity or hyposensitivity (Bruna et al. 2020; Chaplan et al. 1994). More recently, place escape avoidance paradigms and place preference tests have been introduced to better assess the affective or aversive components of neuropathic pain (Hamity et al. 2017; Hamity et al. 2020). Objective measures of nerve damage, like NCS (which assess large axon loss and demyelination) and skin biopsies (used to evaluate small fiber neuropathy), are performed in patients and can be replicated in rodents (Carozzi et al. 2010a, b, 2015; Cavaletti et al. 1991, 2000; Lauria et al. 2005). By comparing these measures between animal models and human patients, researchers can gain crucial insights into disease mechanisms that are difficult to obtain directly from patients.

In animal models, mechanical and thermal (cold and heat) thresholds can be evaluated to detect the onset of mechanical and/or thermal allodynia. Von Frey filaments, Randal Selitto, and Dynamic Aesthesiometer are the most frequently used methods to evaluate mechanical pain threshold and mechanical allodynia. Cold allodynia is measured with the Cold Plate test, the acetone test, the cold water tail immersion test, and the cold plantar test. The Hot Plate test, the Thermal Radiation Method, the Hot Bath Tail Immersion Test, and the Hargreaves test are useful to assess the heat allodynia (Jiang et al. 2025).

Animal models of neuropathic pain have been characterized for the majority of neurotoxic chemotherapy drugs. Researchers use two main types of animal models to study CIPN: acute and chronic, each designed to reflect different aspects of the condition. Acute CIPN models involve administering chemotherapy drugs only once or a few times consecutively. These models are effective for replicating the early, temporary painful symptoms that patients often experience shortly after chemotherapy. A classic example is the cold hyperalgesia reported by patients just hours after an oxaliplatin injection.

In contrast, chronic CIPN models involve repeated injections of chemotherapy drugs over several weeks. These models are crucial for understanding the established peripheral nerve damage that underlies the typical features of long-term painful peripheral neuropathy. In these chronic models, researchers observe a range of issues, including neurophysiological abnormalities, decreased intraepidermal nerve fiber density, neuropathological changes in peripheral nerves and DRG, behavioral signs like mechanical allodynia hyperalgesia, or hypoesthesia, as well as thermal hyper- or hypoalgesia.

However, animal studies have shown that chemotherapy-induced neurotoxicity is not confined to the peripheral nervous system but is able to induce indirect alterations of transmission through the spinal cord and somatosensory system (Carozzi et al. 2013; Lessans et al. 2019; Renn et al. 2011). The spinal electrophysiology is a useful technique to investigate the processes involved in the development of neuropathic pain providing information related to functional indirect changes in central neurons and in their environment produced by a direct damage of peripheral nerves. CIPN animal models are characterized by ectopic discharges and spontaneous action-potential firing in primary sensory afferents, which accordingly produce sensitization of the spinal neurons. This generates an excess of their excitability, which coupled with a decrease of inhibition, results in spinal hyperexcitability, typical of neuropathic pain conditions. This spinal hyperexcitability, beside behavioral alterations of animals, was demonstrated for bortezomib, cisplatin, and oxaliplatin (Carozzi et al. 2013; Lessans et al. 2019; Renn et al. 2011).

Furthermore, as peripheral neuropathies drive ascendant, supraspinal neuronal activity in the somatosensory system is now emerging as a potent tool for analyzing the involvement of central nervous system in neuropathic pain of peripheral origin (see below, paragraph 6).

The features of the main painful CIPN models, together with molecular mechanisms of disease, are described in the following sections.

5.1 Oxaliplatin

Oxaliplatin can be injected in mice and rats at doses ranging between 2 and 10 mg/kg, i.p. or i.v., as single or repeated treatment with cumulative doses spanning from 2 to 40 mg/kg (reviewed in Jiang et al. 2025), and the neuropathic syndromes can be classified into acute and chronic types. Acute models involve a single or short-term high dose injection of oxaliplatin and manifest with alterations in sensory thresholds (cold-induced paresthesia) and muscle spasms immediately after infusion. The primary mechanism is the dysregulation of ion channels as sodium, potassium, and calcium channels, which alter the membrane potential producing spontaneous neuronal firing. The chronic models utilize repeated low-dose injections and manifest with nerve and DRG morphological and functional damage, reduction of intraepidermal nerve fiber density (IENF), associated with altered mechanical and thermal thresholds (Marmiroli et al. 2017a; Pozzi et al. 2020). For detailed schedules, see Jiang et al. 2025. The mechanisms of neurotoxicity (Figure 2) involve consequences of accumulation of oxaliplatin in DRG due to the lacking of a robust blood–nerve barrier, producing the formation of platinum-DNA adducts, mitochondrial dysfunction, alterations in mitochondrial DNA replication, oxidative stress, neuroinflammation, activation of glial cells (astrocytes and microglia) in the spinal cord, which release proinflammatory cytokines, amplifying the pain signal (Cheng et al. 2023; Kim 2020).

5.2 Cisplatin

Rat and mice models of cisplatin-induced neurotoxicity and neuropathic pain have been developed injecting the drug at concentration ranging between 2 and 3 mg/kg i.p., once or twice a week, for 4–5 weeks. Some researchers demonstrated that with a cumulative dose of 6–12 mg/kg, rats showed an abnormal NCS, abnormal altered mechanical nociception, and a nociceptive hypersensitivity to heat (Carozzi et al. 2010a; reviewed in Li et al. 2025; Ta et al. 2009). However, some researchers did not evidence any alteration of the pain behavior in rats treated with a chronic (2 mg/kg, i.p., twice a week for 4 weeks) schedule of injection (Zippo et al. 2024). This could be reasonable since also in patients, the peripheral neuropathy, often severe, is mainly characterized by sensory ataxia, numbness, paresthesia, and dysesthesia, with no or mild pain symptoms. In mice, cisplatin is injected i.p. at a dose of 2.3 mg/kg once a day for 5 days, with 5 days of rest for 2 weeks (Ta et al. 2009) or bi-weekly for 4 weeks (Carozzi et al. 2010a). The most significant mechanism of cisplatin neurotoxicity (Figure 2) is its binding to nuclear DNA where the accumulated DNA damage triggers the p53-dependent apoptotic pathway, leading to the death of sensory neurons. Cisplatin also has a high affinity for mtDNA, leading to mtDNA adducts, ROS production, energetic failure, protein carbonylation, and antioxidant (glutathione) depletion (Gupta et al. 2022; Podratz et al. 2011).

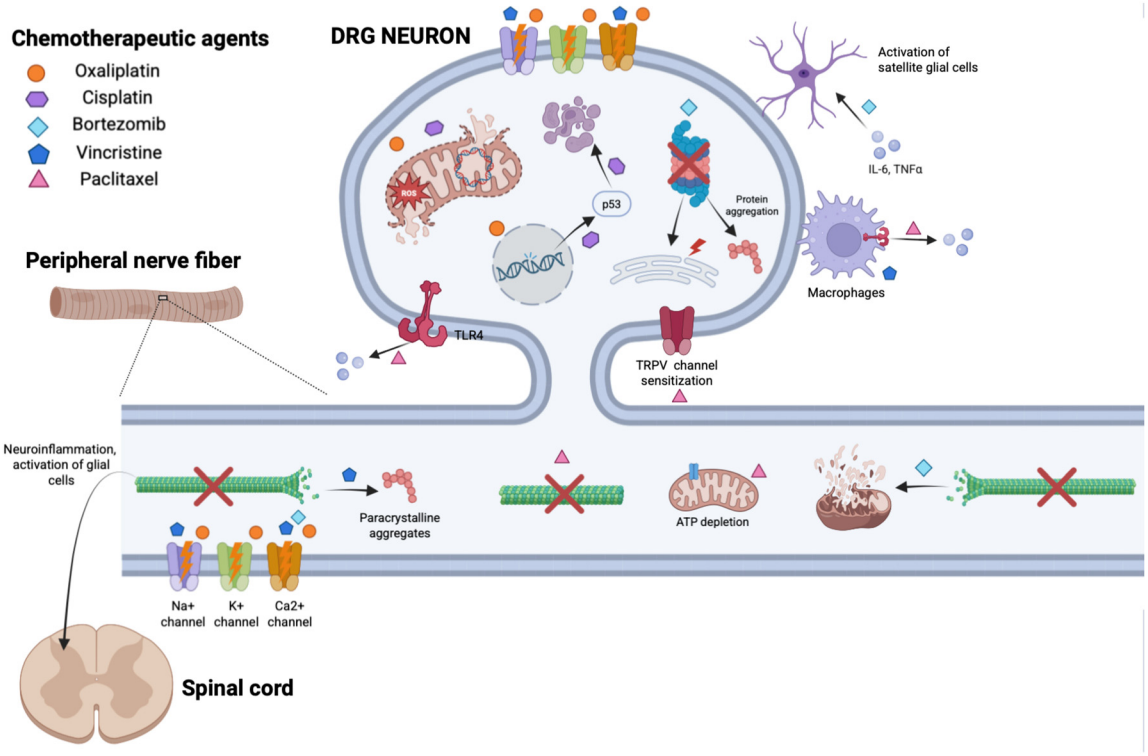

Figure 2: Possible mechanisms of peripheral neurotoxicity of the main classes of antineoplastic drugs.

5.3 Bortezomib

Bortezomib administration in rats typically involves two main regimens: a) short-term, high frequency injections high-frequency dosing of 0.2 or 0.4 mg/kg/day, i.p. or i.v., for 5 days, resulting in a cumulative dose of 1 or 2 mg/kg; this regimen lead to mechanical hyperalgesia and cold allodynia starting around day 5 and persisting for at least 35 days (Duggett and Flatters 2017; Stockstill et al. 2018; Yamamoto et al. 2015). b) Long-term, low-frequency dosing of 0.2 mg/kg, i.v., three times per week for 8 weeks with a cumulative dose of 4.8 mg/kg, which this protocol more closely mimics human dosing, and which involves twice-weekly infusions for 2 weeks, followed by a 10-day rest period to complete a cycle (Quartu et al. 2014). The long-term administration in rats resulted in decreased nerve conduction velocity in the caudal nerve, degeneration of myelinated and unmyelinated axons in the caudal and sciatic nerves, cytoplasmic vacuolization in satellite glial cells surrounding DRG neurons, detachment of satellite glial cells from the nerve cell body, and occasional morphological alterations in DRG neurons (Meregalli et al. 2012, 2015, 2018). Similar findings have been observed in mice, where bortezomib produced nerve degeneration along myelinated and unmyelinated fibers (Alé et al. 2015; Boehmerle et al. 2014; Bruna et al. 2011; Carozzi et al. 2010b, 2013; Geisler et al. 2019). Shorter treatment protocols in mice also induced mechanical hyperalgesia (Ludman and Melemedjian 2019). For a detailed description of treatment regimens, see Geisler et al. (2019). Mechanism of bortezomib neurotoxicity (Figure 2) is multifactorial and involves the inhibition of the 26S Proteasome, which leads to protein aggregation in DRG and ER stress, microtubule dysfunction with swelling and vacuolation of mitochondria within axons (that leads to impaired axonal transport), oxidative stress, dysregulation of calcium homeostasis with calcium overload and cytoskeletal alterations, and increased cytokine release (TNFalfa, IL6), which triggers the activation of satellite glial cells in the DRG and promotes an enhancement of the excitability of nociceptors, contributing to the “burning” neuropathic pain (Argyriou et al. 2014; Carozzi et al. 2015; Staff et al. 2013).

5.4 Vincristine

The most common rodent model for vincristine-induced peripheral neuropathy involves two cycles of five daily i.p. injections of 0.1 mg/kg vincristine, followed by a 2-day rest period. It is characterized by mechanical and thermal hyperalgesia, hyper-responsiveness of C-fibers, neuroinflammation in the sciatic nerve, DRGs, and spinal cord. Furthermore, ultrastructural examination reveals swelling

of myelinated and unmyelinated axons with cytoskeletal changes, such as disorganized microtubules, decreased microtubule density, and abnormal neurofilament clustering in the axoplasm (Tanner et al. 1998; Topp et al. 2000). Other models involve different dosing schedules as 0.75–1.7 mg/kg vincristine i.p. twice weekly for 4 weeks in mice with developed pronounced mechanical hyperalgesia, mild thermal hyperalgesia, axonal degeneration, and neuroinflammation in the peripheral nervous system (PNS). Similar results were seen in rats, with, with a weekly i.v. administration of 0.2 mg/kg vincristine for 4 weeks that led to decreased sensory and motor nerve amplitude, axonal degeneration in the caudal nerve, loss of IENF, and a dose- and time-dependent increase in serum neurofilament levels, indicating axon injury (Meregalli et al. 2018). For a review of the treatment schedules, see Geisler et al. (2019). The primary scientific mechanisms for vincristine-induced neurotoxicity (Figure 2) include the inhibition of microtubule polymerization with the formation of paracrystalline aggregates that in neurons lead to destruction of cellular framework and disruption of axonal transport, alteration of ion channels expression (sodium and calcium channels) related to neuronal hyperexcitability, neuroinflammation with macrophage infiltration of peripheral nerves and DRG, and mitochondrial swelling leading to neuronal energy failure (Li et al. 2020a).

5.5 Paclitaxel

Similar behavioral pain thresholds and nerve alterations are evident for paclitaxel, as reviewed by Bacalhau et al. 2023. Peripheral neuropathy and pain can be induced by injecting paclitaxel i.p. or i.v., at concentrations ranging from 1 to 10, for 4 to 7 alternate or consecutive days (mimicking an acute model of pain) or once a week for 4 weeks, as a faithful resemble of clinical practice (Carozzi et al. 2010b; Zippo et al. 2024). A faithful resemblance of clinical evidence of paclitaxel-induced neurotoxicity was obtained chronically treating animals for several weeks (Carozzi et al. 2010b; Zippo et al. 2024). The neurotoxicity of paclitaxel (Figure 2) is primarily driven by microtubule hyperstabilization and subsequent metabolic and structural collapse, which results in neurons in a “freezing” of the cytoskeleton, axonal degeneration, and axonal transport impairment. Paclitaxel is also uniquely noted for its direct impact on neuronal mitochondria, where it triggers the opening of the mitochondrial permeability transition pore (mPTP), which collapses the membrane potential and leads to ATP depletion. Paclitaxel also significantly alters the electrophysiological properties of peripheral sensory neurons with TRPV (transient receptor potential vanilloid) channels sensitization. It interferes with the innate immune system within the nervous system by activating the TLR4 on both macrophages and sensory neurons and triggering the release of proinflammatory cytokines and chemokines, which recruit more immune cells to the dorsal root ganglia (DRG), perpetuating a cycle of chronic pain (Burgess et al. 2021).

6 Changes in nociceptive modulatory pathways due to neuropathic pain: focus on CIPN

Neuropathic pain induces profound changes in both ascending and descending pain modulatory pathways, leading to complex alterations in pain processing, which occur at multiple levels of the nervous system and involve numerous cellular and molecular mechanisms. These conditions trigger significant modifications in synaptic transmission and neural circuits.

One of the most prominent changes is central sensitization, characterized by increased excitability of the spinal (Carozzi et al. 2013; Renn et al. 2011; Rosenberger et al. 2020) and brain neurons (Finnerup et al. 2021; Ma et al. 2024). This heightened sensitivity involves multiple neuronal mechanisms, including enhanced glutamatergic (particularly through NMDA receptors) and purinergic neurotransmission (including increased P27XR and related PANX channels), reduced inhibitory GABAergic signaling, and altered expression of ion channels (for instance VGSCs). Moreover, many other neurotransmitters’ signalings are involved as summarized in Table 2.

Glutamatergic excitatory synapses represent most of the brain synapses, and the amino acid L-glutamate is essential to regulate synaptic activity striving toward a balance between excitation and inhibition in neural circuits. The most common inhibitory neurotransmitter is gamma-aminobutyric acid (GABA), which can bind to ionotropic GABAA and metabotropic GABAB receptors (Watanabe et al. 2002). Central sensitization has been primarily reported in pain associated cortical regions such as the somatosensory cortices, PFC, ACC, and others (Ji et al. 2018; Ma et al. 2024; Masocha 2016; Thibault et al. 2012).

Increased excitability of glutamatergic pyramidal neurons at the detriment of GABAergic signaling in the mPFC can be considered a key factor for the maladaptive brain processes that lead to increased sensitivity to pain. In this regard, electrophysiological recordings on ACC slices demonstrated a significant increase of excitatory synaptic strength for paclitaxel-treated rats after the onset of

Table 2: Summary of the pathways involved in nociception classified on the basis of the neurotransmitter involved, with indication of the specific molecular alterations and the experimental model employed.

Pathway	Neuropathic changes	Animal model evidence
Noradrenergic	Downregulated α2A-adrenoceptors in locus coeruleus-spinal projections	Zerumbone restores analgesia via α2A agonism in CCI model (Chia et al. 2020)
Opioidergic	Reduced μ-opioid receptor efficacy in periaqueductal gray (PAG)	Stress-induced analgesia becomes opioid-resistant in neuropathic rats (Atwal et al. 2024)
Endocannabinoid	Upregulated CB1 receptor signaling in PAG and rostral ventromedial medulla	JZL195 (endocannabinoid degradation inhibitor) rescues impaired stress analgesia (Atwal et al. 2024)
GABAergic	Decreased GABA synthesis (GAD65/67 downregulation), loss of inhibitory interneurons, impaired KCC2/NKCC1 function	Spinal GABA levels reduced in CCI rats; bicuculline produces allodynia (Li et al. 2019)
Glutamatergic	Enhanced NMDA receptor function (GluN2B subunit), increased AMPA receptor trafficking, mGluR5 upregulation	GluN2B antagonists reduce mechanical allodynia; NMDAR deletion suppresses formalin phase 2 (Liu and Salter 2010)
Serotonergic	Shift from inhibitory to facilitatory modulation, enhanced 5-HT2A/2B/3 receptors, reduced spinal 5-HT content	Descending facilitation in neuropathic pain via 5-HT2A/3 receptors; 5-HT depletion increases CCI sensitivity (Heijmans et al. 2021)
Dopaminergic	Decreased dopamine release in VTA-NAc pathway, reduced D2/D3 receptor binding, impaired motivation circuits	Chronic pain reduces VTA c-Fos and NAc dopamine; progressive ratio responding decreased (Taylor et al. 2016)
Cholinergic	Reduced spinal acetylcholine release, decreased M1 muscarinic and α7 nicotinic receptor expression	α7 nAChR downregulation in spinal cord and sciatic nerve/DRG; nicotinic agonists reduce neuropathic pain behaviors (Di Cesare Mannelli et al. 2014; Zhou et al. 2022)
Purinergic	Enhanced P2X3/P2X4/P2X7 receptor sensitization, increased ATP release from damaged tissues and activated microglia	P2X3 receptor sensitization (3.5-fold increased response) without increased ATP release in SNI (Chen et al. 2005a); P2X7 sensitization requires Pannexin 1 channel activation (Bravo et al. 2022; Di Cesare Mannelli et al. 2015)

neuropathic mechanical allodynia (Nashawi et al. 2016), while the excitatory postsynaptic potentials (EPSPs) slope was reversed to control levels after GABA application to the cortical slices. Increased expression of glutamatergic receptors can further explain glutamatergic system overtake in the mPFC neuronal network. Indeed, enhanced expression of the NMDA subunit NR1 was observed after paclitaxel treatment in mice (Masocha 2015), while upregulation of the GluA1 subunit of the AMPA receptor and the NR2A and NR2B subunits of the NMDA receptor (Alhowail and Aldubayan 2023) was detected consequently to doxorubicin administration in rats. NMDA receptors are permeable to Ca^{2+} influx, which in turn activates calcium/calmodulin-dependent protein kinase II (CaMKII), a serine/threonine kinase that functions as a marker for glutamatergic pyramidal neurons. Ca^{2+} spikes in prefrontal pyramidal neurons are enhanced by paclitaxel treatment (Cao et al. 2022), and the increase of intracellular ions results in activation of CaMKIIα glutamatergic neurons. The hypothesis that cortical hyperactivation paves the way for cancer-related painful neuropathies leads to efforts to study mPFC inhibition in the context of cancer therapy. In one attempt, chemogenic and optogenetic inhibition of glutamatergic CaMKII-positive pyramidal neurons in layer II/III of the mPFC of mice was successful in providing relief against mechanical allodynia and thermal hyperalgesia (Cao et al. 2022).

Activation of supraspinal astrocytes can contribute to central sensitization. Upregulation of GABA transporter-1 (GAT-1), expressed in neurons and astrocytes, in the ACC of paclitaxel-induced neuropathic mice has also been reported (Masocha 2015). Considering the central role of GAT-1 in removing GABA molecules from the synaptic cleft, overexpression of this transporter could result in shortage of GABA at a synaptic level and disruption of GABAergic signaling.

VGSCs are key mediators of nociceptive transmission, and their dysregulation has been implicated in the pathogenesis of neuropathic pain. Changes in their function or expression have been observed primarily in the PNS – especially in DRG – as well as in the spinal cord and other CNS regions. Among the nine alpha isoforms (Nav1.1–Nav1.9), Nav1.7, Nav1.8, and Nav1.9 are highly expressed in DRG, particularly in small-diameter neurons. Alterations in these channels have been reported in various painful neuropathies, including CIPN and hereditary forms (Chen et al. 2025b; Pozzi et al. 2024). In neuropathic pain conditions, altered expression of sodium channels – particularly Nav1.1 and Nav1.3 – has also been observed in different brain regions involved in pain modulation (Chen et al. 2025b), potentially contributing to the hyperactivation of the mPFC observed in cases of CIPN. On this regard, transcript analysis of Nav subunits in the ACC of paclitaxel-treated mouse

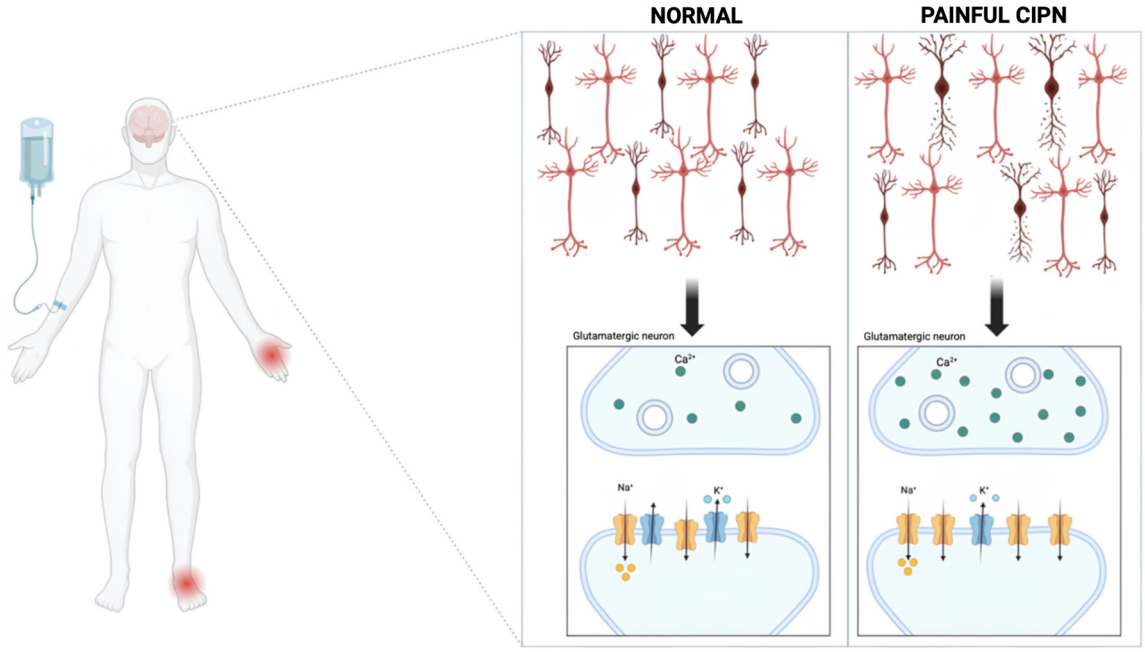

Figure 3: Painful CIPN induces cortical maladaptive alterations characterized by overtake of pyramidal glutamatergic neurons (brown) against GABAergic interneurons (red) activity, as well as increased Ca^{2+} influx in glutamatergic neurons, overexpression of Na^{2+} channels, and downregulation of K^{+} channels.

revealed overexpressed levels of the following subunits: Nav1.1, Nav1.2, Nav1.3, Nav1.6, Nax, and Navb1–Navb4 (Masocha 2016). Accordingly, administration of Nav channel blockers is reported to prevent thermal hyperalgesia and mechanical allodynia in preclinical models of CIPN (Di Girolamo et al. 2025; Li et al. 2018; Webster et al. 2005; Xiao et al. 2008). Nonetheless, clinical trials with selective sodium channel blockers have not produced the expected analgesic outcomes in chronic neuropathic pain (Chen et al. 2025b).

As far as K+ channels are concerned, gene expression analysis of the somatosensory cortex in oxaliplatin-treated rats has brought to light a downregulation of genes coding for voltage-gated K^{+} channels (Kv2.2) associated to an increase of neuronal activation (Cichon et al. 2017; Omran et al. 2021; Thibault et al. 2012; Ziegler et al. 2023). K^{+} channels play a fundamental role in neuronal excitability, and their downregulation implies a lower stimulus for sensory neuronal firing (Tsantoulas et al. 2012).

Since the transition from acute to chronic pain involves complex cellular mechanisms such as the alterations in glutamatergic neurotransmission, with enhanced NMDA and AMPA receptor expression, hyperexcitability in cortical neurons increases sensitivity to noxious stimuli (Kanda et al. 2000). Simultaneously, GABAergic interneuron dysfunction, particularly involving parvalbumin and somatostatin expressing cells, reduces inhibitory tone and promotes pyramidal neuron hyperactivity (Bráz et al. 2012; Cichon et al. 2017). Maladaptive alterations in cortical areas regarding glutamatergic/GABAergic imbalance and altered function of ion channels are represented in Figure 3. Furthermore, GABAergic neurons are more prone to excitotoxic apoptosis due to an increased accumulation of intracellular calcium via the expression of the B-cell lymphoma-extra large mitochondrial transmembrane protein (Jang et al. 2025).

In the context of CIPN, cortical alterations likely represent both compensatory responses to peripheral nerve damage and maladaptive changes that perpetuate chronic pain.

Along with the increased excitability at the spinal and cortical level, abnormal activity in subcortical structures involved in pain transmission and modulation has also been observed. Significant alterations in the descending pain modulatory pathway have been described in neuropathic pain. In particular, key structures such as the PAG, LC, and RVM show modified activity patterns in situations of neuropathic pain.

Single unit recordings in awake-behaving rats treated with paclitaxel captured increased spontaneous firing and burst activity in PAG neurons and enhanced evoked neuronal responses to thermal stimuli, indicating that increased PAG firing activity is involved in the development of paclitaxel-induced neuropathic pain (Samineni et al. 2017). PAG somatostatin (SST) expressing glutamatergic neurons target RVM neurons with excitatory synapses and

are considered to play an important role in enhanced activation of PAG-RVM projections. Accordingly, chemogenetic silencing of PAG SST neurons suppressed oxaliplatin-induced hyperalgesia in mice, while their activation offered a proalgesic effect (Zhang et al. 2023).

RVM and LC, under normal conditions, release serotonin and norepinephrine, respectively, which inhibit nociceptive transmission via activation of 5-HT and α2-adrenergic receptors, but their effectiveness can be reduced in chronic neuropathic conditions.

Alterations in the serotonergic system could be one of the mechanisms responsible for enhanced RVM-dependent pain facilitation. The RVM is one of the richest sources of serotonergic neurons and is the principal provider of 5-HT fibers to the spinal dorsal horn (Wei et al. 2010). Paclitaxel-induced mechanical allodynia in rats was correlated to the hyperactivated state of RVM serotonergic neurons, shown as enhanced p-Erk expression. Increased serotonergic RVM tone was mirrored in the spinal dorsal horn, where it targeted the pronociceptive 5-HT3R receptor. Moreover, animal studies have demonstrated that the balance between pain-inhibiting ("OFF cells") and pain-facilitating ("ON cells") neurons in the RVM shifts toward facilitation. This leads to enhanced descending facilitation of pain transmission at the spinal cord level (Costa-Pereira et al. 2020).

In addition, the descending noradrenergic system, particularly the projections from the LC, undergoes functional alterations in neuropathic pain, resulting in reduced noradrenergic tone and contributing to enhanced pain hypersensitivity (España et al. 2024).

A summary of pathways involved in neuropathic pain, according to the neurotransmitter system involved, is reported in Table 2.

7 Alterations of cognitive functions in chemotherapy-induced painful peripheral neuropathy

Numerous clinical and experimental studies have demonstrated an association between neuropathic pain and cognitive dysfunction (Mai et al. 2021; Tyrtyshnaia et al. 2025). Figure 4 maps the pathophysiological modifications occurring at the supraspinal and spinal levels (described below in the text) associated with painful CIPN.

In the context of patients with CIPN, cognitive deficits are generally considered part of the broader phenomenon known as "chemobrain" or "chemo–fog" (CICI), whose main features have been already described in Section 4.

A range of mechanisms have been proposed to underlie this neurotoxicity, including oxidative stress, disruption of the blood–brain barrier (BBB), genetic predispositions, DNA damage, and others (Salat 2020). Nevertheless, the leading hypothesis centers on chemotherapy-induced neuroinflammation, characterized by cytokine dysregulation (the so-called "cytokine storm"), which in turn promotes the generation of reactive oxygen species (ROS). These processes are believed to be among the primary drivers of cognitive impairment associated with chemotherapy (Lal et al. 2024).

Neuroinflammation largely involves activation of microglia and astrocytes. The glial cell population is known to perform fundamental tasks in maintenance of brain homeostasis and regulation of cognitive tasks like memory formation and learning. Microglia engage with neurons through multiple signaling pathways, like BDNF expression and synaptic pruning, to drive experience-derived memory formation (Cornell et al. 2022). Following injury, the increased production of cytokines by activated microglia has been implicated in the impairment of cognitive functions. Immune response activation in the CNS is associated with the onset of neurodegenerative disorders, aging process, and overall neurological decline, therefore promoting the progression of cognitive abnormalities (Elmore et al. 2018; Grant et al. 2023). Several authors have raised the question of whether the initial damage at the peripheral level could be the cause of CNS alterations underlying the development of cognitive deficits, so the pathways through which lesions in the PNS may trigger neuroinflammatory responses in specific regions of the CNS have been investigated. In a recent study, it was shown that mice subjected to sciatic nerve injury exhibited memory deficits that correlated with neuroinflammation in the brain, characterized by the presence of perivascular macrophages, and increased levels of circulating monocytes (Mai et al. 2021). A proportion of these monocytes were found to transmigrate into the perivascular spaces of the brain – particularly within the hippocampal region – where they were subsequently converted into perivascular macrophages implicated in the neuroinflammatory process. This monocyte-to-macrophage differentiation appears to be mediated by CXCL12 (C-X-C motif chemokine ligand 12), a chemokine known to direct monocyte migration and differentiation. These findings are supported by evidence that elevated levels of circulating monocytes and CXCL12 in the plasma of patients with chronic pain correlate with memory impairment (Mai et al. 2021). Studies on paclitaxel-induced neurotoxicity suggest that, since paclitaxel has a low ability to cross intact BBB, the activation of central glia would be indirectly caused by inflammation originating from the PNS rather than by direct damage from the chemotherapy agent (Grant et al. 2023).

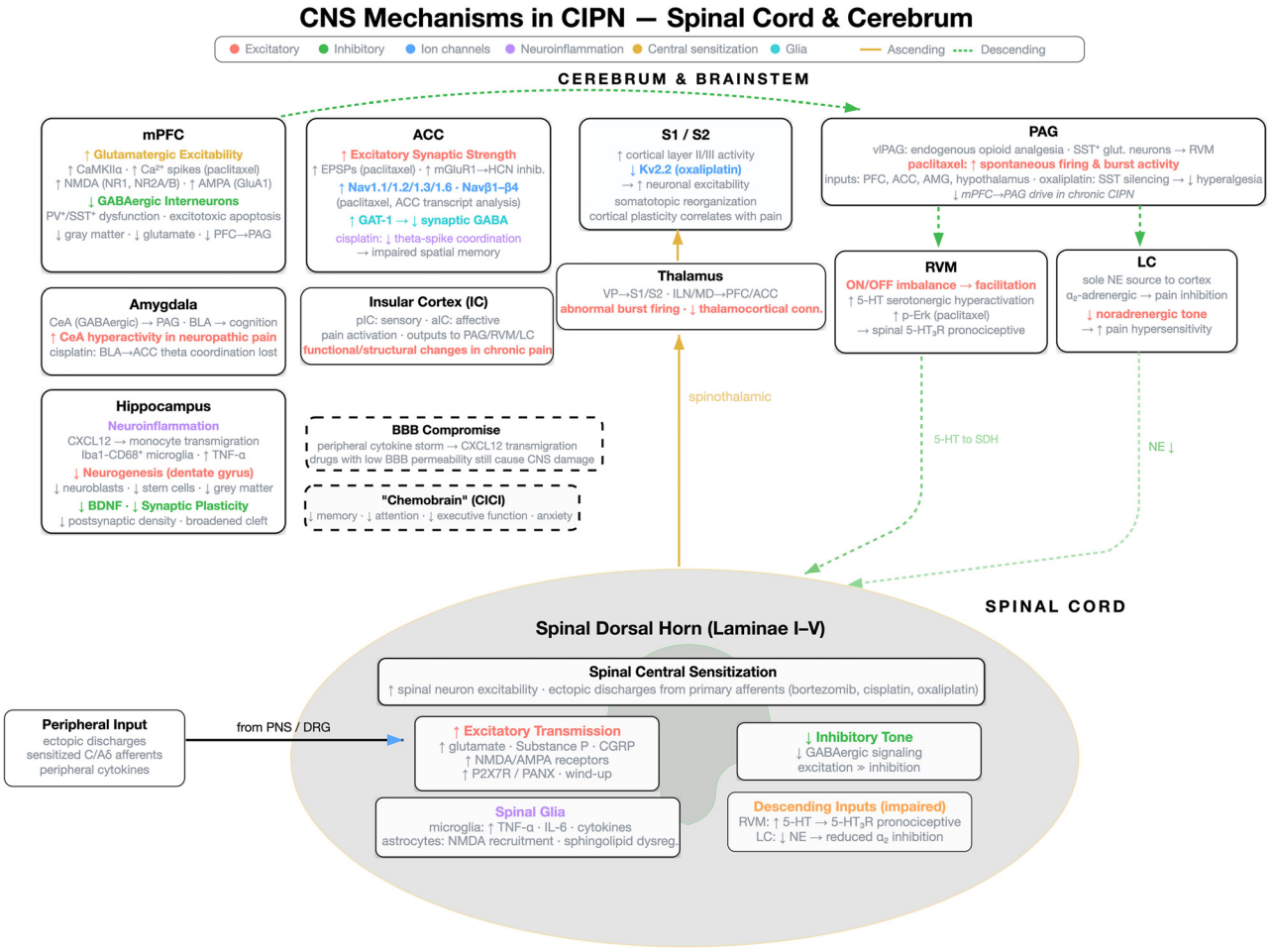

Figure 4: Schematical representation of brain and spinal cord maladaptive changes occurring during painful CIPN. The figure summarizes maladaptive alterations across supraspinal and spinal pain–related regions, including increased excitatory transmission, reduced inhibitory tone, altered ion channel expression, central sensitization, neuroinflammation, glial activation, blood–brain barrier (BBB) disruption, and impairment of descending pain modulatory pathways. At the supraspinal level, changes involving the mPFC, ACC, S1/S2, insular cortex, amygdala, thalamus, PAG, RVM, LC, and hippocampus are associated with abnormal pain processing and chemobrain-related features. At the spinal level, peripheral input from injured primary afferents promotes dorsal horn hyperexcitability through enhanced glutamatergic and purinergic signaling, reduced GABAergic inhibition, activation of spinal glia, and defective serotonergic and noradrenergic descending control. Ascending and descending pathways are indicated, and colors identify the main pathogenetic mechanisms represented in the scheme. Only relevant connections with respect to the topics of the work have been represented.

Paclitaxel-induced nerve injury may promote spinal reorganization underlying central sensitization, with the microglial response arising either from degeneration of central afferent terminals or from spinal factors released by injured neurons (Masocha 2016).

Given that the surge of central inflammation likely results from the spreading of peripheral inflammation across the BBB, this could be assumed as an underlying mechanism of CICI (Cheung et al. 2015; Kesler et al. 2013). Consequently, experimental modulation of glial cells activation and cytokine release in preclinical models of CIPN has been employed to understand the role of neuroinflammation pathways on cognitive impairments. Pharmacological inhibition of TNF-ʎ in paclitaxel-treated rats restored learning and memory performance during the Morris Water Maze test (Li et al. 2018). In the context of a chronic doxorubicin treatment in mice, where a decline in episodic recognition memory was observed, the depletion of Iba1-CD68+ microglia and inhibition of proinflammatory factors overexpression were able to revert this mnemonic impairment (Allen et al. 2019). Similarly, inhibition of M1 microglia polarization (Tang et al. 2022) and targeted microglia depletion in the hippocampus of paclitaxel-treated mice (Grant et al. 2023) were successful in restoring hippocampal-dependent memory performance. BDNF is a neurotrophin ubiquitous to the CNS that plays a pivotal role in neurogenesis, neuronal survival, and differentiation; it also plays a significant role in synaptic plasticity and stimulates actin polymerization to

regulate and shape dendritic spine structure (An et al. 2008). Decreased BDNF levels were observed in brain tissue of mice treated with paclitaxel and methotrexate (Geraghty et al. 2019; Grant et al. 2023), and this is notable because of microglia role in experience-driven memory encoding through BDNF production (Cornell et al. 2022). Thus, microglial inhibition of BDNF expression can have detrimental consequences for memory-acquisition abilities (Parkhurst et al. 2013). Abnormal microglial activation, together with the previously described disturbances in neurotransmission, leads to neuronal dysfunction and impaired synaptic plasticity.

Maladaptive modulation of synaptic transmission in cognition-related brain networks, like hippocampus, ACC, and BLA, are potential mechanisms behind chemotherapy-induced cognitive impairment. Functional synaptic plasticity is favored by episodes of theta band (4–10 Hz) oscillations of local field potential (LFP) in cognition-related brain networks, and the coordination of single-neuron spike activity with theta band oscillations enables memory formation and attention (Cao et al. 2016; Rutishauser 2019). As such, it was demonstrated that cisplatin can disrupt LFP by enhancing theta spectral power and decreasing the phase coordination between theta oscillations and single-unit spikes in the ACC of rats (Mu et al. 2015), resulting in a display of impaired spatial memory. Indeed, cisplatin administration generates a loss of coordination in the basolateral BLA-ACC axis, given that theta burst stimulation from the BLA failed to elicit LFP in the ACC (Mu et al. 2015).

Significant paclitaxel-induced damage to synaptic structures was observed in mice brains through electron microscope analysis, which highlighted a broadening of the synaptic cleft and lowered postsynaptic density, thickness, and length in hippocampal neurons. In accordance, decreased hippocampal BDNF expression level painted a picture of deteriorated synaptic plasticity (Tang et al. 2022). Other studies also reported BDNF levels deficiency in hippocampal tissue of mice following acute paclitaxel treatment (Sung et al. 2021) or chronic treatment with doxorubicin (Usmani et al. 2023); consequently, pharmacological BDNF stimulation improved hippocampal dependent memory performance.

Brain imaging studies represent a valuable *in vivo* approach for investigating the alterations in cerebral regions involved in pain processing.

Resting-state functional MRI (rs-fMRI) can be employed to evaluate changes in functional connectivity among different brain regions, while positron emission tomography (PET) is commonly used to study neuroinflammation by using radioligands targeting the 18-kDa translocator protein (TSPO). TSPO is expressed in central and peripheral immune cells; therefore, both central and peripheral neuroinflammatory processes can be investigated. Some studies have reported elevated brain TSPO signals in patients with chronic low back pain (Loggia 2024). Moreover, studies employing integrated PET/MRI have shown that brain TSPO levels were associated with the strength of functional connectivity between different brain regions (Albrecht et al. 2021).

A key aspect underlying structural brain plasticity is represented by neurogenesis, a process that occurs across adult life in the dentate gyrus of the hippocampus, a fundamental area for learning and memory formation, and in the subventricular zone of the lateral ventricles. The creation of new neural cells supports normal brain function and neuroplasticity and is triggered as a brain healing response after injury or disease (Zhao et al. 2008). The integrity of adult neurogenesis processes is fundamental in learning and memory integration circuitry, while the functional impairment of this process can result in a deterioration of cognitive abilities and the insurgence of mood disorders (Alonso et al. 2024). Neuroimaging studies have reported structural abnormalities and relevant gray matter density reduction in the hippocampus of cancer patients that also displayed difficulties in verbal memory performance, episodic memory, and attention deficits; the association between reduced hippocampal volume and cognitive decline has been ascribed to decreased neurogenesis (Bergouignan et al. 2011; Kesler et al. 2013). Neural cell division reduction can be attributed to direct cytotoxic effects following the administration of chemotherapeutic agents that pass through the blood–brain barrier. However, also drugs that do not cross the BBB or do so in limited quantity can equally affect adult neurogenesis (Janelsins et al. 2010), since they can elicit a peripheral activation of the immune response, meaning that the enhanced circulation of proinflammatory cytokines can be deemed responsible for altered hippocampal neurogenesis (Wang and Jin 2015).

Several authors reported alterations in neurogenesis following treatment with different antineoplastic drugs in animal models. In mice treated with paclitaxel, impairment in spatial memory and learning abilities was observed and correlated with a decreased population of proliferating neuroblasts in the dentate gyrus (Sung et al. 2021). Also, reduction of neural stem cells and immature neurons in the dentate gyrus following chronic doxorubicin treatment in mice was observed (Usmani et al. 2023). A causal relation between cisplatin treatment and impaired working-memory and spatial memory performances was also observed in mice (Chiu et al. 2017) and rats (Lomeli et al. 2017). After a single administration of methotrexate, mice displayed decreased levels of immature progenitor neurons in the

dentate gyrus tissue starting from 12 h and up to the 14th day after treatment (Yang et al. 2011). Marked toxicity against neurogenic cell population was observed also after cyclophosphamide administration in mice, where abnormal dendritic morphology and a lower count of newly born hippocampal neurons were observed, together with impaired spatial recognition and stimuli association memory (Christie et al. 2012).

Overall, cognitive disturbances are frequently observed in patients with CIPN and neuropathic pain, although their underlying causes remain largely unknown. CIPN animal models represent a valuable tool for further investigating this form of neurotoxicity affecting both the peripheral and central nervous systems.

8 Conclusions

The purpose of this review consists in expanding the focus of CIPN pathomechanisms to also include CNS dysregulation, specifically to circuital alterations in supraspinal pain pathways and cognitive impairments associated with anticancer treatment. The limitations on available and recommended treatments for CIPN patients, so far including only symptomatic relief by duloxetine administration, explain the need for new mechanism-based alternatives targeting central dysfunction in the face of CIPN resistance treatment. It is advisable that future research endeavors will address alterations of synaptic transmission in pathways of pain regulation and cognitive impairments among the outcome measures, considering also whether the pathomechanisms manifest differently depending on the anticancer drug administered. An important question that has not found a definitive answer yet regards drawing a clear cause–effect picture among direct peripheral neurotoxicity, neuropathic pain, and CNS comorbidities affecting CIPN patients. The evidence gathered so far shows a reciprocal influence of pathomechanisms including peripheral cytokine migration, BBB weakening, neuroinflammation, and synaptic dysfunction. The ongoing debate needs to be supported through more research efforts in both the clinical and preclinical settings, defining the cascade of events arising from peripheral neurotoxicity and culminating into cognitive dysfunction and chronic sensorial disturbances in CIPN.

Acknowledgments: All figures were generated by “Biorender.” “Compilatio,” the official tool for plagiarism check of the University of Milan Bicocca, was employed.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: L.C., V.A.C., and P.M. conceptualized the review and contributed to the initial title proposal. L.C, A.Z, V.A.C, L.F., and P.M drafted the initial manuscript. L.F and L.C created the figures and proofread the references. V.A.C and P.M thoroughly edited the manuscript and provided structural and linguistic improvements to refine the content. L.C and A.Z. revised and finalized the title. V.A.C and P.M. supervised the project and guided the overall development and direction of the review. A.Z. provided critical feedback. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: AI was minorly employed to improve the language.
Conflict of interest: The authors state no conflict of interest.
Research funding: Italian Ministry of University and Research, PRIN 2022 ID 2022NBS28K, PI Valentina A. Carozzi. Italian Ministry of University and Research, PRIN PNRR 2022 ID P2022C5P3F, PI Antonio Zippo. Italian Ministry of University and Research, PRIN 2022 ID ZL4JP8, Paola Marmiroli, participant.
Data availability: Not applicable.

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