FUTURITY
Medicine

Citation article: Lysetskyi, B., Kobyletskyi, O., Shchybovyk, D., Zubova M., Litvin, O. Neuroplasticity in the pathogenesis and treatment of chronic pain syndrome: new research and therapeutic perspectives. *Futur Med [Internet].* 2024;3(1): 45-58. Available from: https://doi.org/10.57125/FEM.2024.03.30.05

Neuroplasticity in the pathogenesis and treatment of chronic pain syndrome: new research and therapeutic perspectives

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Abstract

Recent research and therapeutic outlooks examine the impact of neuroplasticity on the progression and management of chronic pain syndrome.

Aims: To review neurobiological basis as well as neuroplastic mechanisms in chronic pain syndrome, exploring bidirectional relationship and innovative therapies and to evaluate efficacy/safety of diverse treatments like TENS, rTMS, pharmacotherapies, and exercise in chronic pain management.

Study design: A narrative literature review.

Place and Duration of Study: 2019 to 2024.

Methodology: A narrative review was conducted using the keywords “Neuroplasticity" AND "Chronic Pain" on PubMed yielded a total of 333 publications. Out of the total publications, 21 were deemed directly relevant, probably providing valuable perspectives on the link between neuroplasticity and chronic pain.

Results: Results showed that out of the 11 studies analysed, 7 investigated the bidirectional relationship between chronic pain and neuroplasticity. Additionally, 4 studies reviewed pharmacological methods, 2 studies discussed personalised management and mechanistic profiling, and 7 explored neuromodulation and non-pharmacological interventions. Various neurophysiological correlates of chronic pain were studied, including somatosensory and cortical neurophysiology profiles but Central sensitisation and neuroinflammation were the explored key mechanisms. Activity-dependent plasticity, neuroplasticity in pain modulation, and cortical plasticity are extensively explored, revealing changes in neural activity, synaptic strength, and brain structure. Research explores the connection between chronic pain and neuroplasticity, examining how they impact each other and highlighting the constant interaction between pain perception and neural plasticity. Innovative therapeutic strategies include neuromodulation techniques, pharmacological interventions, personalised pain management, and multimodal approach. Non-invasive brain stimulation, transcutaneous electrical nerve stimulation , and home-based focused tDCS show promise in chronic pain management.

Conclusion: In summary, these findings highlighted the multifaceted nature of chronic pain and the on-going efforts to develop effective therapeutic interventions, showcasing a dynamic field of research aiming to improve the lives of those suffering from chronic pain.

Keywords: Neuroplasticity, pathogenesis, treatment, chronic pain syndrome, research, therapeutic perspectives.

Received: November 24, 2023
Revised: December 2, 2023
Accepted: February 27, 2024
Published: March 11, 2024

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DOI: https://doi.org/10.57125/FEM.2024.03.30.05

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Introduction

Chronic pain is characterised by persistent painful feelings lasting over three months without actual tissue damage or disease. Approximately 20% of the population suffer from chronic pain at any one moment [1]. The chronic pain syndrome is a debilitating condition that is characterised by pain that severely impacts individuals' daily lives and persistent for long time. In 2016, nearly fifty million people in the US suffered from chronic pain which is lasting at least three months or more, resulting in substantial healthcare costs and reduced productivity. This was increased, equivalent to 51.6 million individuals, were affected by chronic pain by 2021. Out of these 17.1 million people endured severe chronic pain, significantly blocking their ability to carry out daily activities. This condition was especially common among individuals who identified as bisexual, as well as those who were divorced or separated. All healthcare providers and organisations should be diligent in addressing health disparities and providing accessible, affordable, diverse, coordinated, and effective pain treatment for everyone [2].

Chronic pain syndrome poses a significant challenge to modern medicine, affecting millions worldwide and often resisting conventional treatments. In recent years, the knowledge of the fundamental processes involved in chronic pain has progressed, with a growing recognition of the brain's incredible capability to adapt and rewire in reaction to different stimuli and damages, proving to be a vital factor in the persistence of chronic pain. This is termed as neuroplasticity.

Recent studies concerning neuroplasticity have shed light on the intricate mechanisms underlying chronic pain, particularly in the context of neuropathic pain stemming from nerve damage. This exploration has led to the recognition of a phenomenon termed oncoplastic pain, emphasising the role of altered neuronal circuits in processing nociceptive signals. This differentiation is essential for determining if pain is caused by direct damage to the nervous system or if it is a result of neuroplastic changes after an injury. Furthermore, this deeper understanding of neuroplasticity has paved the way for the development of novel therapies and treatments for chronic pain. By targeting specific neuronal pathways and mechanisms involved in pain processing, researchers have been able to devise interventions aimed at modulating neuroplasticity to alleviate chronic pain symptoms. These emerging therapies offer promising avenues for individuals suffering from debilitating conditions like neuropathic pain, offering optimism for improved and customized approaches to management in the years ahead [3].

Within the realm of chronic pain treatment, there is growing interest in enhancing neuroplasticity as a promising avenue. Techniques like intermittent fasting and administering glucose have been proposed to fine-tune the balance between synaptic excitation and inhibition, fostering adaptive neuroplastic alterations. These interventions hold potential to enhance treatment efficacy for chronic pain sufferers. By integrating strategies that bolster neuroplasticity with conventional treatments, there's potential to mitigate the maladaptive plasticity linked with chronic pain and ultimately enhance patients' overall well-being [4]. Neuroplasticity plays a crucial role in chronic pain, research has shown that changes in the brain play a significant role in the development and continuation of this condition. Microglia, the immune cells of the central nervous system, are pivotal in this process. They modulate neurons to regulate synaptic pruning, creation, and transmission, thus influencing the development of pain. [5]. Chronic pain is believed to stem from changes in cortical-limbic circuitry, leading to the formation of novel patterns of learning and memory [6]. Sustained and intense stimuli capable of inducing neuroplastic alterations in the peripheral and central nervous systems can lead to the establishment of sensitisation, resulting in enduring and persistent pain [7]. Moreover, detrimental neuroplasticity may cause the brain and nervous system to become too sensitive and overactive to typical stimuli, leading to chronic pain. Recent research delved into neuroplasticity's role in chronic pain syndromes like psoriatic arthritis (PsA) and hand osteoarthritis (hand-OA) and highlight heightened pain sensitisation, psychological distress, and disability in these patients, particularly those with comorbid fibromyalgia. New therapeutic opportunities for chronic pain management are emerging through advancements in understanding neuroplastic changes [8].

Innovative therapeutic strategies are emerging to rewire maladaptive neural circuits and restore balance to the pain processing system. These include neuromodulation techniques, targeted pharmacotherapy, and cognitive interventions, such as intermittent fasting and glucose administration, which have been shown to promote neuroplasticity and potentially optimise chronic pain treatments [9]. Assessing the effectiveness and safety of several treatments, such as Transcutaneous Electrical Nerve Stimulation (TENS), repetitive Transcranial Magnetic Stimulation (rTMS), pharmacotherapies, and exercise routines, is essential for controlling chronic pain. A significant hurdle in this journey lies in the interconnected relationship between chronic pain and neuroplasticity. Chronic pain not only triggers neuroplastic changes, but also sustains them, resulting in a repetitive cycle of pain and impaired function. In order to properly deal with this intricate situation, treatments should aim to address both the perception of pain and the fundamental changes in neural connections [10]. An further obstacle is the heterogeneous character of chronic pain syndromes, which hinders the adoption of a standardised therapeutic approach. Chronic pain refers to

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a range of disorders that have several underlying causes, such as neuroplastic changes occurring in the brain and nervous system. It is crucial to customise treatments in order to fit the unique variations in neuroplasticity patterns and pain experiences of individuals, as this is necessary for obtaining effective management [11]. Neuroplasticity-based treatments for chronic pain offer potential benefits such as rewiring maladaptive neural circuits, enhancing treatment efficacy, promoting adaptive changes, reducing central sensitisation, enabling personalised approaches, and providing long-term relief. Harnessing neuroplasticity holds promise for addressing persistent pain and improving overall outcomes in pain management [12].

This narrative review, titled "Neuroplasticity in the pathogenesis and management of chronic pain syndrome: recent advancements and therapeutic outlook, offers a comprehensive examination of emerging insights into the role of neuroplasticity in both the development and treatment of chronic pain. By integrating recent research findings, it sheds light on the complex mechanisms underlying neuroplastic changes in chronic pain conditions, enhancing our understanding of their origins. Furthermore, the review discusses cutting-edge therapeutic strategies that harness neuroplasticity, proposing new opportunities for groundbreaking interventions focused on regulating neural circuits and revitalising healthy pain perception. Serving as a timely resource, this review caters to clinicians, researchers, and policymakers navigating the dynamic landscape of chronic pain management.

Research Problem

Chronic pain poses a significant challenge in healthcare due to its complex and multifaceted nature, often resistant to conventional treatments. Exploring the intricate neurobiological processes and their interaction with neuroplasticity is crucial for developing effective interventions to manage chronic pain and improve patient outcomes.

Research Focus

This study sought to delve into the complex interaction between neurobiology and chronic pain, with a specific focus on several critical factors. These included central sensitisation, neuroinflammation, adenosine modulation, disparities in somatosensory and cortical neurophysiology, as well as the manifestation of central neuropathic pain. Moreover, the study aimed to investigate the involvement of neuroplastic mechanisms, such as synaptic plasticity, cortical reorganisation, and activity-induced changes in excitability, in both the initiation and persistence of chronic pain conditions. By scrutinising these elements, the research endeavoured to pinpoint novel therapeutic approaches for effectively managing chronic pain while also assessing the safety and efficacy of diverse treatment modalities.

Research Aim and Research Questions

Research Aim

1. Review and analyse the current literature on the neurobiological basis of chronic pain, focusing on central sensitisation, neuroinflammation, adenosine modulation, somatosensory and cortical neurophysiology differences, and central neuropathic pain.
2. Investigate the role of neuroplastic mechanisms, including synaptic plasticity, cortical reorganisation, and activity-dependent changes in excitability, in the development, maintenance, and modulation of chronic pain conditions.
3. Examine the bidirectional relationship between chronic pain and neuroplasticity, exploring how chronic pain drives neuroplastic changes and how neuroplasticity, in turn, influences the persistence and exacerbation of chronic pain.
4. Identify innovative therapeutic strategies for managing chronic pain, including neuromodulation techniques, pharmacological interventions targeting specific neurotransmitter systems, personalised pain management approaches, and treatments based on neuroplasticity mechanisms.
5. Evaluate the efficacy and safety of various treatment modalities in alleviating chronic pain symptoms and improving patient outcomes.

Research Questions

1. How does neuroinflammation contribute to the pathophysiology, and what are the potential targets for anti-inflammatory interventions in pain management?
2. How does cortical reorganisation, including changes in functional connectivity and cortical map reorganisation, contribute to alterations in pain perception and chronic pain development?
3. What neurobiological mechanisms underlie the interaction between chronic pain and neuroplasticity, and how do they contribute to the maintenance of chronic pain states?

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4. How can treatments based on neuroplasticity mechanisms, such as cognitive-behavioural therapy or mindfulness-based interventions, be integrated into multidisciplinary pain management programs to enhance their effectiveness in chronic pain management?
5. What is the comparative efficacy of different neuromodulation techniques in reducing, improving and enhancing quality of life in chronic pain patients?

Research Methodology

General Background

The ability of the brain to reorganise and adapt in response to different experiences, which is essential in managing chronic pain conditions, is known as neuroplasticity. Recent studies have shown the intricate relationship between neuroplasticity processes and chronic pain, providing new treatment possibilities for treating this incapacitating illness.

Chronic pain disorders encompass enduring pain that extends beyond the typical healing time-frame of tissues, often resulting in maladaptive changes within the nervous system. Neuroplasticity mechanisms, such as synaptic plasticity, cortical restructuring, and activity-induced alterations in excitability, play pivotal roles in chronic pain. Central sensitisation, exacerbates pain signals and contributes to heightened pain sensitivity observed in chronic pain syndromes.

The discovery of neuroplastic changes that contribute to chronic pain has driven the creation of cutting-edge treatment methods. Leveraging neuroplasticity pathways offers alternative strategies for pain management beyond traditional analgesic medications. Neuromodulation therapies like transcranial magnetic stimulation and transcranial direct current stimulation have the potential to modulate cortical excitability and disrupt detrimental neuroplastic alterations associated with chronic pain. Additionally, cognitive-behavioural therapy interventions harness neuroplasticity to modify pain perception and bolster coping mechanisms, offering promising avenues for holistic pain management.

In conclusion, neuroplasticity plays a central role in the management of chronic pain syndromes. By elucidating the underlying neurobiological mechanisms and exploring novel therapeutic perspectives, researchers aim to improve pain management strategies and enhance the quality of life for individuals suffering from chronic pain.

Sample / Participants / Group

An extensive review of the literature was conducted. The keyword search "Neuroplasticity" AND "Chronic Pain" on PubMed yielded a total of 333 publications. Among these, 192 publications were found to fall within the time-frame of 2019 to 2024. Notably, 105 of these publications were available as free full text, offering open access to researchers and the public alike. Language specifications were provided for 104 publications, indicating the diverse linguistic landscape of the articles. Additionally, 55 publications were relevant to specific varieties, suggesting a focus on the relationship between neuroplasticity and chronic pain. Out of the total publications, 21 were deemed directly relevant, likely contributing significant insights into the intersection of neuroplasticity and chronic pain as shown in Figure 1. These statistics provided a comprehensive overview of the volume, accessibility, language distribution, and relevance of publications on this subject area on PubMed during the specified period.

Instrument and Procedures

This narrative review utilised a systematic methodology to collect, evaluate, and consolidate pertinent literature on the overlap between "Neuroplasticity" and "Chronic Pain"." The instrument used for this review is PubMed, a widely recognised and comprehensive database of biomedical literature. The search strategy involved the use of specific keywords ("Neuroplasticity" AND "Chronic Pain") to identify pertinent articles published within the defined time-frame of 2019 to 2024.

The procedure involved several key steps:

- The search terms "Neuroplasticity" AND "Chronic Pain" were entered into the PubMed search bar. This focused search query is designed to bring up articles that specifically discuss the connection between neuroplasticity and chronic pain, helping to streamline the literature review process.
- A date filter was applied to restrict the search results to articles published between 2019 and 2024. This time-frame ensured the inclusion of recent research while capturing a substantial volume of relevant literature.
- The initial search results were screened based on the relevance to the review's focus. Articles that did not directly address the relationship between neuroplasticity and chronic pain were excluded during this screening process.

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- For articles passing the initial screening, full-text versions were obtained and thoroughly assessed to determine their suitability for inclusion in the review.
- Relevant data, were extracted from the selected articles. This process involved careful scrutiny of each publication to identify pertinent information that contributes to the narrative review.
- The extracted data were synthesised and analysed to identify common themes, trends, and insights across the selected literature.
- The synthesised findings were critically evaluated to assess the strength of evidence, identify gaps in the literature, and highlight areas for further research.

By following this systematic approach, this narrative review aimed to provide a thorough examination of the role of neuroplasticity in the pathogenesis and treatment of chronic pain syndromes, offering valuable perspectives and implications for clinical practice and research.

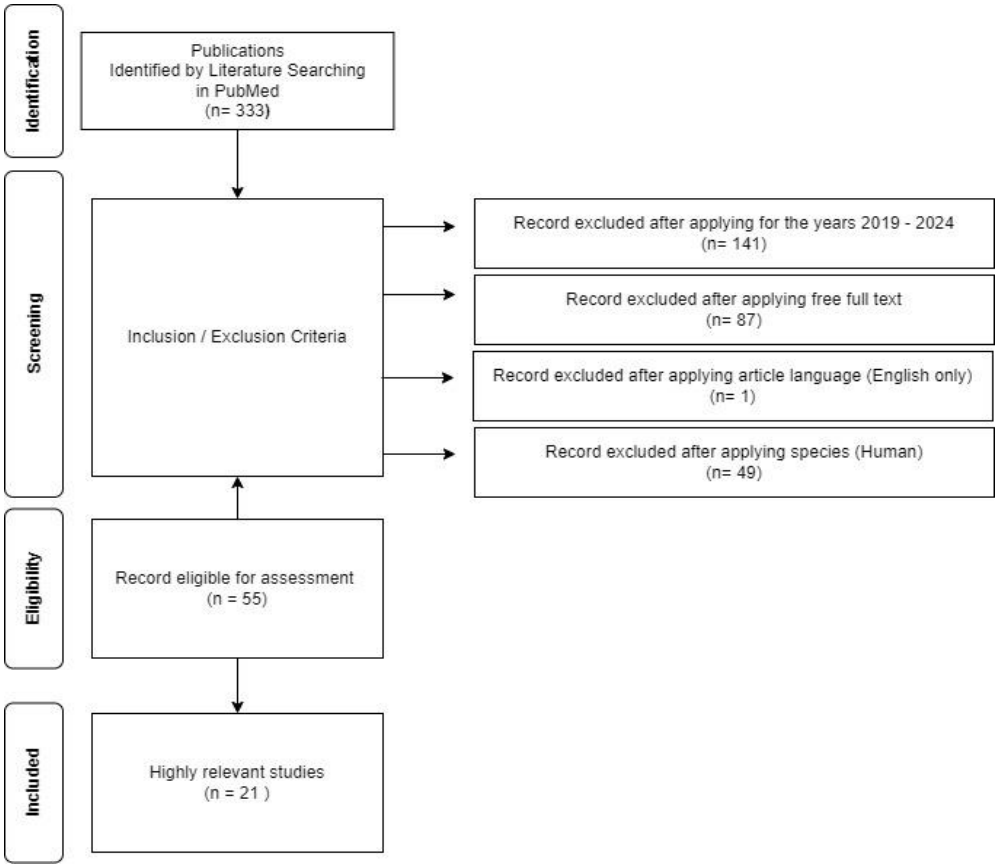

Figure 1. PRISMA flow diagram

Data Analysis

In data analysis for this narrative review, several key steps were involved to extract meaningful insights from the gathered literature on the intersection of "Neuroplasticity" and "Chronic Pain."

- Synthesis of Findings:
  - Integrate and synthesise data extracted from individual articles to develop a cohesive narrative.
  - Highlight key findings, theories, and research methodologies employed in the literature.
  - Provide a narrative review of the current understanding of neuroplasticity in chronic pain pathogenesis and treatment.
- Comparative Analysis:
  - Compare and contrast different studies based on methodologies, sample populations, and research outcomes.
  - Identify consistencies, discrepancies, and areas of agreement or disagreement among the literature.
  - Evaluate the strength of evidence supporting various hypotheses and conclusions.
- Interpretation of Results:
  - Interpret the analysed data in the context of existing theoretical frameworks and conceptual models.
  - Discuss the implications of the findings for understanding the neurobiological basis of chronic pain and informing therapeutic interventions.
  - Address limitations of the literature and suggest directions for future research.
- Data visualization:

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- Utilise visual aids such as tables, graphs, to present key findings and comparisons.
- Enhance the clarity and accessibility of the data analysis process for readers.

Research Results

Figure 2 illustrates the frequency distribution of various study designs within a dataset or literature review. The data categorise studies into different types of research designs commonly encountered in academic literature and scientific research. Among these categories were review articles, which provided comprehensive summaries of existing research, comprising 5 articles. Clinical trials, which assessed the efficacy and safety of medical interventions in humans, were represented by 5 studies. Systematic reviews or meta-analyses, which synthesised data from multiple studies, were included with a count of 2. Experimental studies, involving controlled manipulation of variables to establish causation, were represented by 1 study. Finally, observational studies, where researchers observed subjects in their natural environment to identify associations between variables, made up the majority with 8 studies. This distribution offered insight into the variety of research approaches utilised to investigate different phenomena or topics within the dataset.

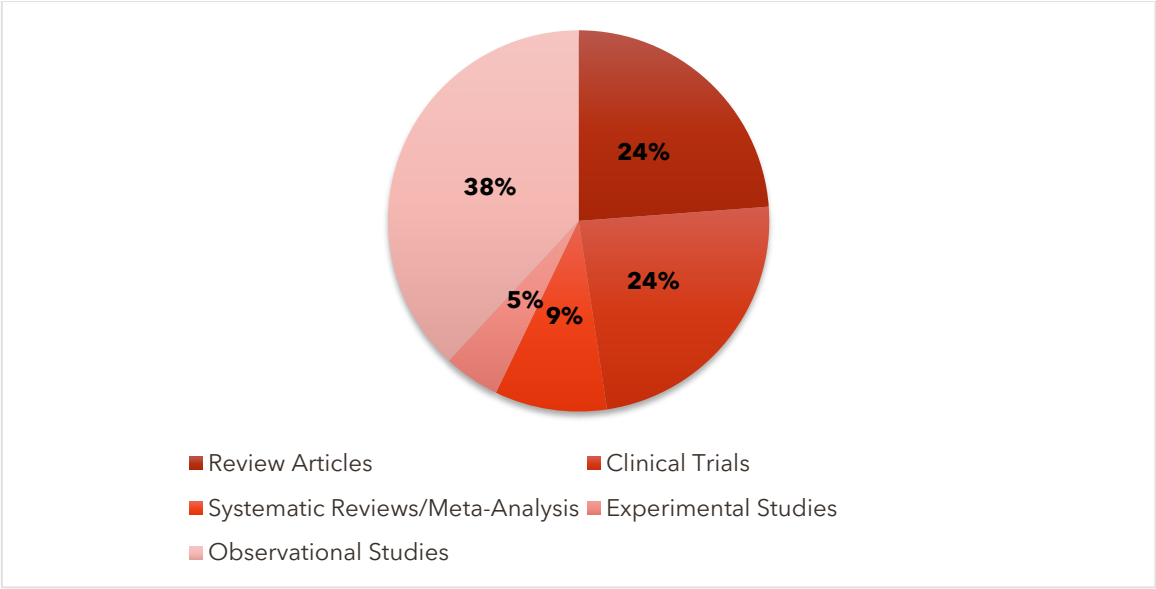

Figure 2. Frequency distribution of study design

Table 1 shows the results of the neurobiological basis of chronic pain, categorised into several groups and subgroups. The first group, "Mechanisms of Chronic Pain," explores central sensitisation, neuroinflammation, adenosine modulation, aging-related neuroinflammation, changes in pain processing brain areas, and also its impact on brain [9,13–20]. The second category, "Specific Pain Conditions and Modalities," covers a range of chronic pain conditions and treatment approaches. This includes discussing different types of chronic pain related to Parkinson's disease, central neuropathic pain, phantom limb pain, the use of TENS interventions, chronic low back pain, and exploring the correlation between BDNF levels and clinical pain assessments in older individuals with knee osteoarthritis. It also covers the role of neuroplasticity and neurotrophins in chronic pain, along with the association between sensory and motor cortex characteristics and chronic low back pain [21–27]. The third group, "Neural Circuits and Pathways," focuses on the involvement of neural circuits and pathways in chronic pain, including contemporary pain science theories, biological underpinnings, and underlying neural pathways [28–32]. The fourth group, "Treatment and Modulation," discusses treatment approaches and modulation techniques for chronic pain, highlighting duloxetine's modulation of central pain mechanisms [33]. Lastly, the fifth group, "Pain Network and Interaction," touches upon the interaction within the pain network [34]. Each subgroup is accompanied by a frequency count indicating the number of occurrences, providing a structured overview of the neurobiological aspects of chronic pain, along with references for further exploration and research.

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Table 1. Neurobiological Basis of Chronic Pain

Groups	Subgroup	Frequency	Reference
Mechanisms of Chronic Pain	Central sensitisation and neuroinflammation Adenosine modulation Underlying neurobiological mechanisms of chronic pain Aging-related neuroinflammation Changes in brain areas due chronic pain. Neurobiological mechanisms underlying chronic pain Effects of long-term opioid use Interaction between sleep impairments and central pain pathways	9	[9,13–20]
Specific Pain Conditions and Modalities	PD-related chronic pain subtypes with distinctive somatosensory and cortical neurophysiology profiles Central neuropathic pain Phantom limb pain and TENS interventions Chronic low back pain and impaired anti-nociceptive mechanisms BDNF and clinical pain measures in older adults with knee OA Role of neuroplasticity and neurotrophins in chronic pain Association between characteristics of sensory and motor cortices and chronic low back pain	7	[21–27]
Neural Circuits and Pathways	Involvement of neural circuits in chronic pain Contemporary pain science theories Biological underpinnings, Underlying neural pathways, And neurological mechanisms in chronic pain	5	[28–32]
Treatment and Modulation	Duloxetine's modulation of central pain mechanisms	1	[33]
Pain Network and Interaction	Pain network interaction	1	[34]

Table 2 outlines various neuroplastic mechanisms, categorising them into distinct subcategories, and provides information on their frequency of occurrence along with references. The first subcategory, "Activity-dependent Plasticity," encompasses changes in neural circuits and connections in response to activity patterns and experiences [13,18,29,33,34]. The second subcategory, "Neuroplasticity in Pain Modulation," focuses on adaptive changes in neural pathways related to the perception and regulation of pain [14,23–25,30,31]. Lastly, "Cortical Plasticity in Chronic Pain" is the third subcategory, specifically addressing changes in cortical regions associated with chronic pain conditions [9,15,19–22,26,27,32]. The references cited in each subcategory correspond to the studies or sources that have investigated or discussed these neuroplastic mechanisms.

Table 2. Neuroplastic Mechanisms.

Category	Subcategories	Frequency	Reference
Neuroplastic Mechanisms	Activity-dependent Plasticity	5	[13,18,29,33,34]
	Neuroplasticity in Pain Modulation	6	[14,23–25,30,31]
	Cortical Plasticity in Chronic Pain	9	[9,15,19–22,26,27,32]

Table 3 depicts the multifaceted relationship between chronic pain and neuroplasticity through categorisation based on the focus of the studies. The group titled "Bidirectional Relationship Between Chronic Pain and Neuroplasticity" (Frequency: 11) delves into studies exploring the reciprocal influence between chronic pain and neuroplasticity, suggesting a feedback loop wherein chronic pain induces neuroplastic changes while neuroplasticity mechanisms can exacerbate pain experiences [9,13,15,18,23–25,28–30,32]. Additionally, the "Impact of Neuroplasticity on Chronic Pain" group (Frequency: 5) concentrates on how neuroplasticity mechanisms directly affect chronic pain, implying their crucial role in pain development and maintenance [16,21,26,33,34]. The "Neuroplasticity Modulation Techniques in Chronic Pain" category (Frequency: 3) examines interventions targeting neuroplasticity to alleviate chronic pain symptoms [17,18,24]. One study, represented in the "Neuroplastic Changes in Chronic Pain Conditions" group (Frequency: 1), delves into specific neuroplastic alterations associated with chronic pain [19]. Finally, a single study falls under the "Indirect Examination of Neuroplasticity in Chronic Pain" category (Frequency: 1), suggesting an indirect exploration of neuroplasticity's role in chronic pain management [27]. This categorisation provides a comprehensive understanding of the varied aspects of the relationship between chronic pain and neuroplasticity, shedding light on potential avenues for research and intervention.

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Table 3. Bidirectional Relationship Between Chronic Pain and Neuroplasticity

Group	Frequency	Reference
The Reciprocal Interaction Between Chronic Pain and Neuroplasticity	11	[9,13,15,18,23–25,28–30,32]
Impact of Neuroplasticity on Chronic Pain	5	[16,21,26,33,34]
Neuroplasticity Modulation Techniques in Chronic Pain	3	[17,18,24]
Neuroplastic Changes in Chronic Pain Conditions	1	[19]
Indirect Examination of Neuroplasticity in Chronic Pain	1	[27]

Table 4 presents a comprehensive overview of innovative therapeutic strategies categorised into four distinct groups. The first group focuses on Neuromodulation Techniques and Non-Pharmacological Interventions, encompassing approaches such as transcranial direct current stimulation and high-definition tDCS targeting specific brain regions to enhance pain management. Additionally, interventions like exercise therapy, BDNF-blocking therapies, and sleep therapy are explored to normalise pain sensitivity [13,19,20,22–25]. The second group, Pharmacological Interventions and Targeted Therapies, involves strategies like targeting adenosine receptors and specific neurotransmitter systems, alongside techniques such as optogenetics or chemo genetics to modulate neural circuits. This group also delves into unconventional methods to optimise the neurobiological environment for improved pain responsiveness. Acupuncture and spinal manipulative therapy are highlighted as potential interventions, possibly in combination with nerve growth factors, for various diseases [9,14,26,28]. Personalised Pain Management and Mechanistic Profiling, the third group, advocates for tailoring treatments based on individual pain subtypes and neurophysiology profiles, considering cognitive aspects and clinical pain [22,33]. Finally, Multimodal and Comprehensive Approaches emphasise combining pharmacological and non-pharmacological interventions to address chronic pain comprehensively, targeting specific neurobiological or neuroplastic mechanisms [16,32]. Each strategy is supported by references, indicating the scientific literature where these approaches have been discussed or studied. Overall, the table underscores the diversity and innovation in addressing chronic pain, spanning from neurological interventions to personalised, patient-centric approaches.

Table 4. Innovative Therapeutic Strategies

Groups	Strategies	Frequency	Reference
Neuromodulation Techniques and Non-Pharmacological Interventions	Neuromodulation approaches, BDNF-inhibiting treatments, and physical activity interventions, Modulated TENS patterns as potential alternatives to conventional sensory neurostimulation tDCS as a therapeutic intervention Using HD-tDCS to target the mPFC for improving descending pain inhibitory function Pharmacotherapies targeting glutamate homeostasis and behavioral interventions such as Mindfulness-oriented recovery enhancement (MORE) Sleep therapy	7	[13,19,20,22–25]
Pharmacological Interventions and Targeted Therapies	Targeting adenosine receptors for pain management Targeting specific neurotransmitter systems, modulating neural circuits using optogenetic or chemogenetic techniques, and exploring novel treatment modalities to restore the balance between reward and anti reward systems Intermittent fasting and glucose administration Pharmacotherapy targeting glutamate homeostasis and behavioral interventions such as Mindfulness-oriented recovery enhancement (MORE) Acupuncture and SMT, could lead to innovative therapeutic strategies. Potential synergistic use of nerve growth factors with acupuncture and SMT in neurological, endocrine, and immune diseases	4	[9,14,26,28]
Personalised Pain Management and Mechanistic Profiling	Individualised pain management strategies based on pain subtype and neurophysiology profiles Tailored Pain Care: Mechanistic Profiling, Cognitive Influences, and Clinical Insights	2	[22,33]
Multimodal and Comprehensive Approaches	Multimodal approaches integrating pharmacological and non-pharmacological interventions Managing or alleviating chronic pain by targeting specific neurobiological or neuroplastic mechanisms	2	[16,32]

Discussion

This narrative review showed that the majority of studies were observational (8), followed by review articles and clinical trials (both 5), systematic reviews/meta-analyses (2), and experimental studies (1). This highlighted the

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diversity of research approaches used to investigate topics. This further provides a structured overview of the neurobiological basis of chronic pain, highlighting mechanisms, specific conditions, neural pathways, treatment modalities, and network interactions. Central sensitisation, neuroinflammation, and adenosine modulation emerge as key mechanisms, alongside conditions like PD-related pain and chronic low back pain.The understanding of neural circuits and pathways is crucial, as indicated by contemporary pain science theories. Latest New research explores the prevalence and risk factors of de novo widespread musculoskeletal post-COVID pain in non hospitalised patients and reveal a 5.3% occurrence rate, with older age, female sex, higher BMI, and specific medical histories identified as risk factors.Recognising these factors underscored the need for tailored pain management techniques for those experiencing symptoms [35]. Similarly, similar research explores neuroplasticity's role in chronic pain syndrome development and treatment and showed that understanding brain changes could lead to innovative therapies. This perspective offers hope for managing post-COVID chronic pain, especially among vulnerable groups, potentially enhancing their quality of life amid the pandemic's ongoing challenges [36]. Treatment insights include duloxetine's modulation of central pain mechanisms. This study also evaluates various treatment modalities, such as electrical nerve stimulation and pharmacotherapy, in alleviating chronic pain symptoms and improving patient outcomes. Other investigations have shown that chronic pain arises as a result of persistent pain lasting more than three months owing to damage to the somatosensory nerve system from injury or illness. The global prevalence of this issue is on the rise, causing significant concern. Patients experience sudden pain, hyperalgesia, and strange sensations as main symptoms, affecting both physical and mental health, ultimately reducing their overall quality of life. While the precise cause of CNP is not fully understood, studies indicate that the central sensitisation, peripheral sensitisation, neuroinflammation, defective nociceptive modulatory systems, oxidative stress responses, glial cell activation, and psychosocial variables play crucial roles. This page seeks to summarise the latest research on CNP's neurological underpinnings, providing valuable information for future efforts in illness prevention and treatment [37,38]. A recent research demonstrates the rising occurrence of chronic pain and the inadequate therapy available, emphasising the need for a more profound comprehension of its neurological foundation. Employing reverse translational research may help uncover pathways, create treatments, and progress clinical trials. Recent studies have highlighted the role of the emotional limbic brain in linking nociception and pain perception, as well as in the transition from acute to chronic pain, underscoring its increasing importance in the field [39]. The latest literature highlights the pivotal role of brain-derived neurotrophic factor in chronic pain, elucidating its involvement in central sensitisation, neuroinflammation, and synaptic plasticity. Elevated BDNF levels in chronic pain disorders suggest its potential as a biomarker and therapeutic target, offering new avenues for treatment strategies [40].

The neuroplasticity is the brain's capacity to adjust and restructure its functions and form in reaction to various stimuli such as learning, experiences, injuries, or environmental alterations. The brain may alter its synaptic connections, neuronal pathways, and cellular architecture via several means. The neuroplasticity is crucial in influencing the brain growth, learning, memory, and rehabilitation from damage or illness. It includes changes in the strength and effectiveness of synaptic connections between neurons, known as synaptic plasticity. The neuroplasticity may play a role in the creation and persistence of many neurological and mental disorders. Experiencing persistent discomfort. While discussing various neuroplastic mechanisms, this study emphasised the activity-dependent plasticity, neuroplasticity in pain modulation, and cortical plasticity in chronic pain. Activity-dependent plasticity highlights neural circuit changes due to activity and experiences, while neuroplasticity in pain modulation addresses adaptive alterations in pain-related neural pathways. Cortical plasticity in chronic pain focuses on changes in cortical brain regions linked to prolonged pain states. These mechanisms are supported by numerous references, indicating their significance in neuroscience research. Understanding these neuroplastic processes provides valuable knowledge about how the brain can adapt to various stimuli and contribute to the onset of chronic pain disorders. This understanding can guide the development of effective therapeutic interventions. Similarly, another research concerning structural neuroplasticity demonstrates that this kind of neuroplasticity entails alterations in the neural connections in the central nervous system. The term typically refers to the brain's capacity to alter its neural connections. This highlights functional neuroplasticity, which refers to changes in the brain's functional structure, including modifications in the effectiveness of synaptic connections between neurons. It refers to the process of altering the brain's functioning to operate differently from its prior state [41]. Different research on homologous area adaptation indicates that this kind of neuroplasticity takes place during the first crucial stage of development. If a certain brain module is injured early in childhood, its functions might relocate to other brain regions unaffected by the impairment. This study explored cross-modal reassignment, map expansion, and compensatory masquerade in relation to sensory information reorganisation, sensory map enlargement, and alternative task strategies in the brain [42].

Current narrative review categorises studies on chronic pain and neuroplasticity, revealing a bidirectional relationship where pain induces neural changes, influencing pain perception, and vice versa. Other researches also emphasises neuroplasticity's pivotal role in chronic pain, offering potential targets for intervention. Techniques modulating neuroplasticity show promise in pain management. Indirect examinations suggest broader implications of neuroplasticity in pain processing. These findings underscore the intertwined nature of chronic pain and

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neuroplasticity, urging further exploration for improved understanding and treatment strategies. The bidirectional relationship between chronic pain and neuroplasticity involves a dynamic interplay where chronic pain can induce neuroplastic changes in the central nervous system, affecting synaptic connectivity and brain function. Conversely, neuroplasticity mechanisms, such as synaptic remodeling, can impact the chronic pain. Similarly, several studies have carefully investigated this association, with research concentrating on changes in neural circuits, neurotransmitter systems, and brain areas involved in pain processing [43]. Furthermore, therapeutic interventions like repetitive transcranial magnetic stimulation or transcranial direct current stimulation have been studied to reduce chronic pain. [44,45]. Additionally, Research has investigated the neuroplastic alterations related to chronic pain in the brain and spinal cord, revealing how chronic pain affects neuroplasticity and results in ongoing pain problems. Studies have shown a two-way connection between back pain and serious depression in US adults, indicating a shared neuroplasticity process that underlies their link [46]. A combined analysis of two national aging cohort studies has further supported the connection between pain and symptoms of depression, indicating that individuals with pain are at a higher risk of developing depressive symptoms and vice versa [47,48]. These studies provide vital insights into the complicated link between chronic pain and neuroplasticity, highlighting the interaction between persistent pain conditions and the brain's adaptive modifications.

The current narrative review also outlines innovative therapeutic strategies for chronic pain management, emphasising diverse approaches ranging from neuromodulation techniques to personalised interventions. Neuromodulation methods like tDCS and HD-tDCS target brain regions to improve pain inhibitory function, while non-pharmacological interventions such as exercise and sleep therapy aim to normalise pain sensitivity. Pharmacological interventions, including targeting adenosine receptors and neurotransmitter systems, alongside unconventional strategies like intermittent fasting, offer promising avenues. Personalised pain management based on individual profiles is advocated, along with multimodal approaches integrating pharmacological and non-pharmacological treatments. This review emphasises the changing field of chronic pain treatment by combining scientific progress with patient-focused strategies. While another research explores neuroplasticity's role in chronic pain syndrome it’s pathogenesis and treatment, offering therapeutic insights and indicate neural changes following limb immobilisation, suggesting functional brain reorganisation within 14 days. Connectivity alterations in sensorimotor regions imply potential implications for error detection and motor learning in chronic pain management [49]. This is important to understand how the brain adapts to chronic pain because it offers promising insights into innovative treatment approaches and underscores the importance of targeting neural mechanisms to alleviate chronic pain and enhance patient outcomes [50]. Other research provide insights on non-invasive brain stimulation for managing chronic pain. Neurostimulation methods such as rTMS and tDCS have shown encouraging outcomes in treating several chronic pain syndromes, however the data about their efficacy is still developing. Transcutaneous electrical nerve stimulation has been thoroughly researched for alleviating pain by adjusting nociceptive input at various locations including peripheral, segmental, and extrasegmental sites. Transcutaneous electrical nerve stimulation has shown favorable results in decreasing pain intensity and enhancing sensorimotor function across different situations [51,52]. Another study explored the role of neuroplasticity in chronic pain syndrome particularly in the context of therapeutic interventions like repetitive transcranial magnetic stimulation (rTMS) and highlights the intricate mechanisms of neuroplastic changes at different levels of the nervous system, providing valuable information on how to enhance treatment strategies and identify new directions for research to enhance patient outcomes [53]. Furthermore, the progress in neuromodulation methods such as high-definition tDCS aimed at the motor cortex have been investigated for disorders such as chronic migraine and pain. Home-based targeted transcranial direct current stimulation has been suggested as a viable method to improve the effectiveness of pain treatment in clinical settings. Studies also emphasises the effectiveness of bilateral excitatory M1 stimulation for providing widespread pain alleviation in chronic disorders such as fibromyalgia or chronic migraine [54,55]. Similarly, another study explores the role of neuroplasticity in understanding and treating chronic pain, with a focus on fibromyalgia syndrome and discusses the potential of transcranial direct current stimulation (tDCS) in alleviating FMS pain [56]. While recent research delves into the role of conditioned pain modulation responses in chronic knee pain patients, revealing distinct subgroups with facilitatory or inhibitory CPM patterns. These results indicate possible implications for treatment approaches and underscore the significance of exploring individual variations in CPM responses to better comprehend chronic pain syndromes [57]. Studies indicate that non-pharmacological therapies including acupuncture, yoga, music therapy, and exercise are safe alternatives to medicine for managing chronic pain. They use several methods to reduce pain, encouraging the brain to change and preventing increased sensitivity. It is essential to address constraints such as treatment variability and obstacles to access in order to maximize their effectiveness [58]. There is latest research that highlights the potential of psilocybin in treating refractory Lupus pain through neuroplastic mechanisms, suggesting a novel therapeutic avenue [59]. While recent studies indicate that conditions such as Provoked vulvodynia (PV) involve changes in brain regions responsible for mood, stress, and pain due to neuroplasticity, there is also evidence of gene expression alterations in the amygdala, prefrontal cortex, and periaqueductal gray matter contributing to the development of pain. Treatment with Venlafaxine has been shown to modify these gene expressions, leading to both pain relief and reduced anxiety [60].

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Conclusions and Implications

Several significant findings have emerged regarding the interaction between chronic pain and neuroplasticity. Researches have shown that BDNF plays a key role in central sensitisation and neuroinflammation, with both pro-nociceptive and anti-nociceptive effects. Additionally, studies have emonstrated the efficacy of adenosine in alleviating hyperalgesia and allodynia and identified the differences in somatosensory and cortical neurophysiology profiles related to Parkinson's disease. Central neuropathic pain is associated with distinct neurophysiological alterations, such as reduced motor evoked potentials and impaired short intracortical inhibition. Additionally, interventions such as training-induced neuroplasticity, duloxetine therapy, and repetitive transcranial magnetic stimulation of the motor cortex have demonstrated efficacy in managing chronic pain. Despite these advancements, challenges persist in translating findings from animal models to humans and addressing sex and age differences in preclinical studies. The understanding of the bidirectional relationship between chronic pain and neuroplasticity, as well as the involvement of various neurotransmitter systems and neuroimmune interactions, offers valuable insights for future research and therapeutic interventions.

Implications

Deepening our knowledge of the complex mechanisms that contribute to chronic pain not only helps us understand the root causes of this condition but also has important implications for improving clinical approaches to diagnosis and treatment. Precise diagnostic methods tailored to individual pain subtypes, particularly in conditions like Parkinson's disease, underscore the importance of recognising differences in somatosensory and cortical neurophysiology profiles. Additionally, identifying neural circuits involved in both pain and comorbid psychological symptoms paves the way for personalised therapeutic treatments. Non-pharmacological options such as transcutaneous electrical nerve stimulation (TENS) and innovative strategies like intermittent fasting and glucose administration present alternative approaches warranting further exploration. Moreover, understanding the bidirectional relationship between chronic pain and neuroplasticity emphasises the need for interdisciplinary approaches integrating neurological and psychological perspectives. Finally, the potential for developing novel analgesic agents targeting nociceptive signaling pathways offers promising prospects for more effective pain management strategies.

Declarations

Author Contributions

Conceptualization, Bohdan Lysetskyi and Oleh Kobyletskyi; methodology, Dmytro Shchybovyk; software, Dmytro Shchybovyk; validation, Oleh Kobyletskyi, Mariia Zubova, and Olga Litvin; formal analysis, Mariia Zubova; investigation, Bohdan Lysetskyi; resources, Olga Litvin; data curation, Dmytro Shchybovyk; writing—original draft preparation, Bohdan Lysetskyi; writing—review and editing, Oleh Kobyletskyi and Mariia Zubova; visualization, Olga Litvin; supervision, Bohdan Lysetskyi; project administration, Oleh Kobyletskyi, Mariia Zubova. All authors have read and agreed to the published version of the manuscript.

Funding

Funding information is not available

Institutional Review Board Statement

Not Applicable

Informed Consent Statement

Not Applicable

Conflicts of Interest

The authors declares that there is no conflict of interests regarding the publication of this manuscript.

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