

Article

Neuromodulation in Pain Management for Rehabilitation: Current Status and Future Perspectives

Hao Hu^{1,*}, Fang Liu¹, Wenjuan Wu¹, Yun Luo^{1,2}, Yanbiao Zhong^{1,2} and Maoyuan Wang^{1,2}

- ¹ Gannan Medical University, Ganzhou, Jiangxi, China
- ² Department of Rehabilitation Medicine, First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, China
- * Correspondence: Hao Hu, Gannan Medical University, Ganzhou, Jiangxi, China

Abstract: Neuromodulation techniques have gained significant attention in pain management, particularly in the rehabilitation of chronic pain conditions. These therapies target the nervous system to alter pain perception and promote recovery by modulating neural activity. This review provides an overview of the current state of neuromodulation in pain management, highlighting key techniques such as spinal cord stimulation, peripheral nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation. We also explore the underlying neurophysiological mechanisms, clinical applications, and challenges associated with these therapies. The future of neuromodulation in rehabilitation is promising, with advancements in bioelectronic medicine and personalized, AIdriven approaches offering new opportunities for more effective and tailored treatments. However, challenges such as device accessibility, patient variability, and long-term efficacy need to be addressed to optimize their clinical use. This review concludes by discussing the potential directions for future research and the clinical implications for integrating neuromodulation into comprehensive pain management strategies.

Keywords: neuromodulation; pain management; rehabilitation; spinal cord stimulation; bioelectronic medicine

1. Introduction

Pain is a complex and multifaceted experience involving sensory, emotional, and cognitive components. In the context of rehabilitation, effective pain management is essential for improving functional outcomes and enhancing the quality of life for patients with chronic pain conditions. Neuromodulation has emerged as a promising approach to pain management, offering targeted interventions that alter neural activity through electrical or pharmacological means [1].

Neuromodulation in pain management refers to the modulation of nervous system activity to alleviate pain through various techniques, including spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). These interventions aim to modify pain signaling pathways, promoting analgesic effects and facilitating neural plasticity. Unlike conventional pharmacological treatments, neuromodulation offers a non-opioid alternative, reducing the risk of drug dependence and systemic side effects.

The role of neuromodulation in rehabilitation extends beyond pain relief. By modulating neural circuits, these techniques can enhance motor recovery, improve sensory integration, and optimize functional rehabilitation outcomes. For patients with conditions such as neuropathic pain, post-stroke pain, or spinal cord injury-related pain, neuromodulation provides a crucial adjunct to physical therapy and other rehabilitative interventions [2].

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This review aims to provide a comprehensive overview of the current status and future perspectives of neuromodulation in pain management for rehabilitation. The article will first explore the underlying mechanisms of neuromodulation, followed by a discussion of key neuromodulatory techniques and their clinical applications. Challenges and limitations will be addressed, along with emerging innovations that may shape the future of neuromodulatory approaches in optimizing pain management and functional recovery.

2. Mechanisms of Neuromodulation in Pain Management

2.1. Neurophysiological Basis of Pain Modulation

Pain perception is governed by a series of complex neurophysiological processes. The pain experience is largely mediated by both ascending pain pathways that transmit nociceptive signals and descending pain control systems that modulate these signals at various levels. The descending system, which originates in areas such as the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), has the ability to inhibit or enhance the transmission of pain signals through the spinal cord, essentially determining the intensity of pain experienced. Neuromodulation techniques, by influencing these pathways, can effectively reduce pain.

For instance, spinal cord stimulation (SCS) activates descending inhibitory pathways, thus modulating pain at the level of the spinal cord, while techniques like transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) target central neural regions to modulate cortical processing of pain signals [3].

2.2. Key Neuromodulatory Pathways and Neurotransmitters

The involvement of various neurotransmitters is crucial in pain modulation. Endorphins, serotonin (5-HT), norepinephrine (NE), and gamma-aminobutyric acid (GABA), to name a few, play pivotal roles in pain control. For example, endorphins bind to opioid receptors and inhibit pain signals, while serotonin and norepinephrine are involved in descending pain modulation. GABA, an inhibitory neurotransmitter, helps to suppress pain processing at the spinal and brainstem levels.

Neuromodulation techniques aim to enhance or suppress the activity of these neurotransmitters to relieve pain. For example, SCS and peripheral nerve stimulation (PNS) enhance the action of endorphins and serotonin, leading to pain relief at both the spinal and peripheral levels. TMS and DBS primarily influence glutamate and dopamine pathways in the brain, altering the processing of pain-related information. Table 1 summarizes the mechanisms of neuromodulation and the key neurotransmitters targeted by different techniques.

Neuromodulation Technique	Targeted Path- ways	Key Neuro- transmitters	Mechanism of Action
Spinal Cord Stimu- lation (SCS)	Dorsal horn of the spinal cord	Endorphins, GABA, Seroto- nin	Activates descending inhibitory pathways, reduces nociceptive transmission
Peripheral Nerve Stimulation (PNS)	Peripheral nerves, spinal cord	Serotonin, En- dorphins	Modulates peripheral nerve activ- ity to decrease pain signals
Transcranial Mag- netic Stimulation (TMS)	Cortical motor areas, PAG	Serotonin, Glu- tamate	Alters cortical excitability to re- duce pain perception

Table 1. Summary of Neuromodulation Mechanisms and Targeted Pathways.

Deep Brain Stimula-	Thalamus,	Dopamine, Glu-	Stimulates brain regions involved
tion (DBS)	PAG, RVM	tamate	in pain processing and inhibition
Vagus Nerve Stimu-		Acetylcholine,	Modulates brainstem structures to
lation (VNS)	brainstein, PAG	Norepinephrine	regulate pain pathways

As shown in Table 1, each neuromodulation technique targets specific neural structures and pathways, with varying roles for neurotransmitters. The table outlines the mechanisms of action and the key neurotransmitters involved, providing a comparative overview of these techniques. Notably, techniques like SCS and PNS primarily target the spinal cord and peripheral nerves, while TMS and DBS exert their effects at higher levels of the central nervous system. Understanding these differences is crucial for tailoring pain management strategies to individual patients based on the underlying mechanisms of their pain.

3. Current Neuromodulation Techniques in Pain Management

Pain management in rehabilitation has seen a growing range of neuromodulation techniques. These therapies aim to alter the neural processing of pain through electrical stimulation or other means. Each method has distinct mechanisms of action, clinical applications, and effectiveness, making them valuable for different pain conditions. Below, we discuss the main neuromodulation techniques currently employed in pain management.

3.1. Spinal Cord Stimulation (SCS)

3.1.1. Mechanism of Action

Spinal Cord Stimulation (SCS) involves the implantation of a device that delivers electrical pulses to the dorsal columns of the spinal cord. This electrical stimulation interferes with the transmission of pain signals from the peripheral nerves to the brain. The mechanism relies on the principle of gate control theory, which suggests that stimulating the spinal cord can inhibit pain signals before they reach the brain, thereby providing pain relief.

3.1.2. Clinical Applications and Effectiveness

SCS has been shown to be effective for treating chronic pain conditions, particularly failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and neuropathic pain. Clinical studies indicate that SCS provides significant pain relief in a substantial number of patients, with many experiencing a reduction in opioid consumption. It is often considered when other pain management strategies, such as medication or physical therapy, have not been effective [4].

3.2. Peripheral Nerve Stimulation (PNS)

Peripheral Nerve Stimulation (PNS) involves the implantation of a small electrode near a peripheral nerve to modulate its activity. It has been particularly beneficial for conditions such as chronic headaches, post-surgical pain, and neuropathic pain. The main advantage of PNS is its ability to target specific nerve regions, offering a more localized treatment compared to SCS. Studies have reported successful outcomes, with patients experiencing significant reductions in pain and improvements in quality of life.

3.3. Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS)

Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are non-invasive techniques that use electromagnetic fields or low electrical currents to modulate brain activity. TMS involves the application of magnetic pulses to specific areas of the brain, while tDCS uses a weak direct current to stimulate cortical regions. Both techniques are used to modulate the cerebral cortex, influencing pain perception and inducing neuroplastic changes that may reduce chronic pain. TMS is particularly effective in treating conditions like fibromyalgia, chronic migraine, and depression-related pain, while tDCS has been shown to benefit patients with neuropathic pain and musculoskeletal pain.

3.4. Vagus Nerve Stimulation (VNS) and Deep Brain Stimulation (DBS)

Vagus Nerve Stimulation (VNS) and Deep Brain Stimulation (DBS) are invasive techniques that target the brainstem and subcortical brain structures. VNS involves stimulating the vagus nerve, which affects the brainstem and can modulate pain pathways. DBS targets the thalamus or PAG, areas involved in pain processing. Both methods have been shown to be effective in treating refractory chronic pain, particularly in conditions like trigeminal neuralgia and cluster headaches. DBS, in particular, has been used in patients with Parkinson's disease who also experience significant pain as a secondary symptom.

To provide a clearer comparison of these techniques, Table 2 below summarizes the key aspects of each neuromodulation technique discussed above.

Technique	Mechanism of Action	Indications	Effectiveness	Clinical Applica- tions
Spinal Cord Stimulation (SCS)	Electrical pulses to the dorsal col- umns of the spi- nal cord	Chronic pain, FBSS, CRPS, Neu- ropathic pain	High effective- ness in reducing pain and opioid use	Chronic pain management, Failed back sur- gery syndrome
Peripheral Nerve Stimu- lation (PNS)	Electrical modula- tion of peripheral nerves	Chronic head- aches, Post-surgi- cal pain, Neuro- pathic pain	Effective for local- ized pain reduc- tion	Headache, post- operative pain re- lief
Transcranial Magnetic Stimulation (TMS)	Magnetic pulses to specific brain regions	Fibromyalgia, Chronic migraine, Depression-related pain	Significant reduc- tion in pain per- ception and neu- roplasticity	Non-invasive, treats brain- based pain syn- dromes
Transcranial Direct Current Stimulation (tDCS)	Low electrical current to cortical regions	Neuropathic pain, Musculoskeletal pain	Improvement in pain levels and neuroplastic changes	Non-invasive, used for chronic pain
Vagus Nerve Stimulation (VNS)	Electrical stimula- tion of the vagus nerve	Refractory chronic pain, Trigeminal neuralgia, Cluster headaches	Effective for chronic, refrac- tory pain	Pain manage- ment in neuro- logical disorders
Deep Brain Stimulation (DBS)	Electrical pulses to the thala- mus/PAG	Refractory chronic pain, Parkinson's disease-related pain	Proven efficacy in pain relief	Chronic pain management in neurological dis- eases

Table 2. Comparison of Neuromodulation Techniques in Rehabilitation Pain Management.

By referring to Table 2, we can compare the mechanisms, effectiveness, and applications of various neuromodulation techniques used in rehabilitation for pain management. Techniques such as SCS and PNS primarily target peripheral and spinal pathways, while TMS and tDCS offer non-invasive alternatives to modulate brain activity. Both VNS and DBS are invasive approaches that influence brainstem and deep brain structures, particularly for chronic pain conditions that have not responded well to other treatments. This comparison helps to highlight the strengths of each technique and provides guidance for selecting the most appropriate therapy for different clinical scenarios [5].

4. Clinical Applications in Rehabilitation

Neuromodulation techniques have demonstrated a wide array of clinical applications in the rehabilitation of patients suffering from chronic pain. These techniques are particularly useful in addressing pain that is refractory to traditional pain management approaches. Below, we will explore the use of neuromodulation in managing specific pain conditions commonly seen in rehabilitation settings, including chronic musculoskeletal pain, neuropathic pain conditions, post-stroke pain, and spinal cord injury-related pain [6,7].

4.1. Chronic Musculoskeletal Pain

Chronic musculoskeletal pain (CMP) is one of the most common complaints among individuals undergoing rehabilitation, especially in older adults and those recovering from injury. CMP can be debilitating and often leads to long-term disability. Neuromodulation techniques, such as spinal cord stimulation (SCS) and transcranial direct current stimulation (tDCS), have been effectively used to alleviate this type of pain. These techniques work by modifying the neural pathways that contribute to pain perception and promoting neuroplastic changes in the affected areas. Evidence from clinical trials indicates that these methods can significantly reduce pain intensity, improve functional outcomes, and decrease the need for pharmacological interventions.

4.2. Neuropathic Pain Conditions

Neuropathic pain, resulting from damage to the nervous system, can be one of the most challenging types of pain to manage. This category includes conditions such as post-herpetic neuralgia, diabetic neuropathy, and sciatica. Neuromodulation techniques like peripheral nerve stimulation (PNS) and spinal cord stimulation (SCS) are particularly beneficial in treating neuropathic pain. These methods target the pain pathways at the level of the spinal cord and peripheral nerves, often leading to remarkable pain relief where traditional therapies have failed. In many cases, these techniques reduce the need for long-term opioid use and improve the patient's quality of life [8].

4.3. Post-Stroke Pain and Rehabilitation

Stroke survivors often experience various forms of pain, including central post-stroke pain (CPSP), which is a common complication. This type of pain arises from damage to the central nervous system and is difficult to treat with conventional therapies. Transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) have shown promise in managing post-stroke pain, particularly for patients with CPSP. These techniques work by modulating cortical and subcortical brain regions that are involved in pain processing, helping to alleviate the chronic pain and improve the functional recovery of stroke patients.

4.4. Spinal Cord Injury-Related Pain

Pain resulting from spinal cord injuries (SCI) can be severe and persistent, significantly affecting a patient's rehabilitation process. Spinal cord injury-related pain includes both nociceptive pain from tissue damage and neuropathic pain due to nerve injury. Spinal cord stimulation (SCS) is commonly used for SCI-related pain management, and it has been shown to significantly reduce both types of pain. The ability of SCS to target the spinal cord directly provides patients with a powerful tool for managing chronic pain and improving mobility [9]. To summarize the clinical applications of neuromodulation in rehabilitation pain management, Table 3 below provides a comparison of the neuromodulation techniques used for the different types of pain commonly encountered in rehabilitation settings.

Table 3. Clinical Applications of Neuromodulation Techniques in Rehabilitation Pain Management.

Pain Condition	Neuromodulation Technique	Effectiveness	Clinical Benefits
Chronic Muscu-	Spinal Cord Stimula-	High effectiveness in pain	Decreased pain inten-
loskeletal Pain	tion (SCS), tDCS	reduction	sity, improved mobility
Neuropathic	Spinal Cord Stimula-	Effective in pain relief	Improved quality of
Pain	tion (SCS), PNS	Effective in pain refier	life, reduced opioid use
Post-Stroke Pain (CPSP)	Transcranial Mag- netic Stimulation (TMS), DBS	Significant pain reduction in CPSP	Alleviates central pain, enhances recovery
Spinal Cord In- jury-Related	Spinal Cord Stimula- tion (SCS)	Significant reduction in both nociceptive and neu-	Improved function, re- duced medication de-
Pain		ropathic pain	pendency

As seen in Table 3, neuromodulation techniques have distinct applications depending on the type of pain. Spinal Cord Stimulation (SCS) appears to be particularly effective in treating both chronic musculoskeletal pain and spinal cord injury-related pain, likely due to its ability to target spinal pathways. Peripheral Nerve Stimulation (PNS) is more commonly applied to treat neuropathic pain, where it helps modulate pain signals at the peripheral nerve level. Non-invasive techniques, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), have proven effective in managing central post-stroke pain (CPSP), providing significant relief by targeting cortical and brainstem regions.

Overall, neuromodulation offers a range of effective treatment options for pain management in rehabilitation. These techniques are especially beneficial in cases where traditional pain management strategies, including pharmacological approaches, have failed or caused undesirable side effects. By targeting specific pain pathways and promoting neuroplasticity, neuromodulation has become an invaluable tool in the rehabilitation of patients with chronic pain conditions.

5. Challenges and Limitations

While neuromodulation techniques have shown significant promise in pain management for rehabilitation, there are several challenges and limitations that must be addressed. These obstacles affect both the practical application of these therapies and their long-term effectiveness. Below, we explore three key challenges: technological constraints and accessibility, patient selection and response variability, and long-term efficacy and safety concerns [10].

5.1. Technological Constraints and Accessibility

Neuromodulation therapies, particularly invasive methods like spinal cord stimulation (SCS) and deep brain stimulation (DBS), often involve complex and expensive devices. The need for specialized equipment and skilled practitioners for implantation and maintenance limits the accessibility of these treatments, especially in low-resource settings. Additionally, the high cost of devices and long-term follow-up care may prevent patients from receiving the most appropriate treatment. The lack of standardized protocols for device selection, implantation techniques, and postoperative care further complicates the widespread adoption of neuromodulation techniques [11].

5.2. Patient Selection and Response Variability

Patient selection is a critical factor in the success of neuromodulation treatments. Not all patients are suitable candidates for these therapies, and the outcomes can vary significantly between individuals. For example, spinal cord stimulation may be highly effective for one patient but offer little benefit to another with a similar condition. Factors such as comorbidities, psychological status, and pain characteristics play a significant role in determining the success of treatment. Moreover, the variability in patient response means that there is no guarantee that a neuromodulation technique will work for every individual, making it essential to tailor treatments based on specific patient needs.

5.3. Long-Term Efficacy and Safety Concerns

While neuromodulation therapies can provide significant short-term pain relief, there are concerns about their long-term efficacy and safety. Over time, the effectiveness of some devices may decrease, necessitating reprogramming, battery replacement, or even surgical revision. The long-term safety of invasive neuromodulation techniques, such as SCS and DBS, remains a subject of ongoing research, with potential risks including infection, device malfunction, and nerve damage. Additionally, the cumulative effects of chronic stimulation on the nervous system are not fully understood, raising questions about the potential for adverse effects in the long run [12].

To summarize the major challenges associated with neuromodulation in pain management, Table 4 below highlights the key issues in the field.

Challenge	Description	Impact on Treatment
Technological Con-	High cost of devices and complex	Limits access to treatment, es-
straints and Acces-		pecially in low-resource set-
sibility	implantation procedures	tings
Patient Selection	Not all potionts reason of wall to	Treatment effectiveness var-
and Response Vari-	not all patients respond well to	ies, making it difficult to pre-
ability	neuromodulation treatments	dict outcomes
Long-Term Efficacy	Potential decrease in treatment effec-	Concerns about device lon-
and Safety Con-	tiveness over time, long-term risks as	gevity, side effects, and surgi-

Table 4. Major Challenges in Neuromodulation for Pain Management.

sociated with devices cal complications As summarized in Table 4, the major challenges facing neuromodulation for pain management are multifaceted. Technological constraints and accessibility are perhaps the most pressing, as the cost and complexity of these devices limit their widespread use, particularly in underserved populations. The patient selection and response variability issue underscores the importance of individualized treatment plans, as not all patients experience the same level of benefit. Finally, concerns about long-term efficacy and safety highlight the need for continued research into the sustainability and risks of neuromodulation therapies.

Addressing these challenges will require not only advancements in technology to make neuromodulation devices more accessible and effective but also a more personalized approach to patient care. Furthermore, long-term studies are essential to assess the sustained benefits and potential risks of these therapies, ensuring that neuromodulation remains a viable and safe option for pain management in rehabilitation.

6. Future Perspectives and Emerging Innovations

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As we look toward the future of neuromodulation in pain management, several groundbreaking advancements are on the horizon, which could radically transform rehabilitation approaches. These innovations - bioelectronic medicine, personalized AI- driven neuromodulation, and the integration of neuromodulation with neurorehabilitation strategies — hold the potential to enhance therapeutic efficacy, but each also presents unique challenges that require thoughtful consideration.

6.1. Advancements in Bioelectronic Medicine

The development of bioelectronic medicine is poised to offer novel, highly-targeted interventions for chronic pain by utilizing miniaturized, implantable devices that directly interact with the nervous system. These devices offer precision and the ability to modulate neural activity with greater accuracy, reducing the side effects commonly associated with broader electrical stimulation techniques. However, challenges such as biocompatibility, immune responses, and long-term efficacy need to be addressed before widespread adoption can occur.

In Table 5, we highlight some key advancements in bioelectronic medicine and personalized neuromodulation. These emerging technologies provide tailored solutions that could improve treatment precision but are also hindered by challenges such as device longevity and patient variability.

Future Direction	Description	Challenges
Miniaturized Bioe-	Development of implantable devices to	Biocompatibility, long-
lectronic Devices	target specific neural pathways	term efficacy
Smart and Adaptive	Devices that adjust treatment in real-	Power consumption, de-
Devices	time based on feedback	vice longevity
AI Integration for	AI algorithms to personalize stimula-	Data privacy, algorithmic
Personalization	tion parameters for individual needs	accuracy and fairness

Table 5. Future Directions in Bioelectronic Medicine and Personalized Neuromodulation.

6.2. Personalized and AI-Driven Neuromodulation

Al's potential in personalizing neuromodulation therapies is immense, offering realtime adjustments to treatment plans based on data from various sources such as genomics, neuroimaging, and patient-reported outcomes. This data-driven approach can optimize outcomes, minimize unnecessary interventions, and adapt to the patient's evolving needs. However, the complexity of the human body poses significant hurdles, as algorithms must learn to manage vast amounts of complex and dynamic data. Moreover, the ethical concerns surrounding data privacy and bias in AI models cannot be overlooked.

6.3. Integration with Neurorehabilitation Strategies

Another exciting development is the potential integration of neuromodulation with neurorehabilitation strategies, such as physical therapy and cognitive rehabilitation. This approach could promote neuroplasticity and improve functional recovery, particularly for conditions like stroke and spinal cord injuries. However, achieving effective integration across rehabilitation disciplines is a challenge. Additionally, the timing and synchronization of neuromodulation with rehabilitation interventions must be optimized for maximal benefit, and there may be concerns about patient adherence to complex, multimodal treatments.

7. Conclusion

In summary, neuromodulation has emerged as a transformative tool in the management of pain, particularly within the realm of rehabilitation. From spinal cord stimulation to transcranial magnetic stimulation, a variety of neuromodulatory techniques have demonstrated significant promise in alleviating chronic pain and enhancing recovery outcomes for patients with musculoskeletal, neuropathic, and post-surgical pain. These therapies work by modulating neural circuits that influence pain perception and neuroplasticity, ultimately promoting recovery and improving quality of life.

The mechanisms underlying these therapies are diverse, involving complex neurophysiological pathways and neurotransmitter systems. Techniques such as peripheral nerve stimulation and deep brain stimulation highlight the flexibility of neuromodulation in addressing a wide spectrum of chronic pain conditions. However, despite their effectiveness, the challenges related to patient selection, long-term safety, and device accessibility remain significant hurdles that need to be overcome to ensure widespread clinical implementation.

Looking ahead, the future of neuromodulation in pain management holds exciting possibilities, especially with the rise of bioelectronic medicine and personalized, AI-driven approaches. The integration of these innovations with neurorehabilitation strate-gies could pave the way for more holistic and adaptive treatments, offering greater precision and tailoring to individual patient needs. However, addressing challenges such as biocompatibility, ethical concerns, and interdisciplinary collaboration will be key to realizing the full potential of these technologies.

Future research should focus on refining these techniques, exploring their integration into multi-modal rehabilitation regimens, and conducting long-term studies to better understand their efficacy and safety. There is also a need for more randomized controlled trials and large-scale studies that can provide stronger evidence for their clinical benefits across diverse patient populations.

Clinically, neuromodulation represents a paradigm shift in the management of chronic pain, offering a promising alternative to traditional pharmacological treatments. As the field advances, clinicians will need to stay abreast of new developments and continue to integrate these emerging therapies into comprehensive pain management plans. Ultimately, the goal is to provide patients with more effective, personalized, and sustainable solutions that improve both their functional recovery and quality of life.

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