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Review article

Neuromodulation therapy for phantom limb pain: A review of the current status and future perspectives

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ABSTRACT

Background: Phantom Limb Pain (PLP) is a common and intractable neuropathic pain condition that occurs following limb amputation, significantly impacting patients' quality of life. The prevalence of PLP ranges from 45% to 85%. Traditional pharmacological treatments have limited efficacy and are frequently accompanied by significant side effects.

Objective: This review aims to provide a comprehensive overview of the multi-level pathophysiological mechanisms underlying PLP, synthesize clinical evidence on both invasive and non-invasive neuromodulation techniques, analyze differences in therapeutic outcomes and targets, and offer insights for clinical practice and future research.

Methods: This is a narrative review that integrates the existing evidence and current clinical applications of various treatment approaches for PLP.

Results: The mechanisms of PLP involve peripheral nerve ectopic discharges, cortical reorganization, and the interaction of various psychological factors. The short-term efficacy of invasive treatments, such as spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation, ranges from 14% to 80%. DRG stimulation shows more promise in terms of long-term stability. Non-invasive techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), when combined with mirror therapy, can enhance therapeutic outcomes. Emerging technologies, such as brain-computer interfaces (BCI) and temporally interfering stimulation (TIS), remain in the preclinical phase of investigation.

Conclusion: Neuromodulation techniques offer a multi-dimensional treatment strategy for PLP, with potential improvements through parameter standardization, individualized treatment optimization, validation in multi-center randomized controlled trials, and an overall enhancement of clinical efficacy.

1. Introduction

Phantom Limb Pain (PLP) is a common phenomenon in which patients continue to experience pain or other abnormal sensations in the lost limb following partial or complete limb amputation.[1] The onset and duration of PLP vary across individuals, typically appearing within days to several months post-amputation.[2] Symptoms often manifest as burning, stinging, or electric shock-like sensations, all of which can lead to significant physical and psychological distress.[3] PLP is commonly accompanied by other symptoms, such as phantom limb sensations and movement disorders; however, pain remains the most prominent and debilitating symptom. Epidemiological data suggest that the prevalence of PLP among amputees ranges from 45% to 85%,[4] with chronic cases often resulting in persistent symptoms that severely affect health-related quality of life.

The pathophysiological complexity of PLP, combined with the limitations of traditional therapeutic strategies, renders this condition one of the most persistent challenges in modern pain management. Current

Abbreviations: ACC, anterior cingulate cortex; AI, artificial intelligence; BCI, brain-computer interface ; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; DRG, dorsal root ganglion; EEG, electroencephalography; FMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; M1, primary motor cortex; MT, mirror therapy; PAG, periaqueductal gray; PLP, phantom limb pain; PVG, periventricular gray; PWM, pulse-width-modulated; RMT, resting motor threshold; RTMS, repetitive transcranial magnetic stimulation; SCS, spinal cord stimulation; S1, primary somatosensory cortex; TENS, transcutaneous electrical nerve stimulation; TMS, transcranial magnetic stimulation; TIS, temporally interfering stimulation; VAS, visual analog scale; VPL, ventral posterior lateral; VPM, ventral posterior medial; DCS, transcranial direct current stimulation; TFUS, transcranial focused ultrasound; TPBM, transcranial photobiomodulation

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therapeutic approaches primarily rely on pharmacological treatments, psychological interventions, and surgical procedures. However, these modalities often provide only suboptimal pain relief, accompanied by significant adverse effects, which hinder the achievement of sustained clinical efficacy.[5] This therapeutic deadlock highlights the urgent need for innovative and well-tolerated intervention strategies. The convergence of cutting-edge technologies in biomedical science has driven the development of neuromodulation as a promising alternative to conventional therapies. These techniques target pain signal transduction pathways by precisely modulating neural circuit activity. Clinically, neuromodulation approaches are categorized into invasive and non-invasive methods, each offering distinct therapeutic potential for managing refractory PLP. Techniques such as deep brain stimulation (DBS), spinal cord stimulation (SCS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) have shown varying degrees of efficacy in clinical studies.[6] Nonetheless, ongoing gaps in knowledge regarding the sustainability of long-term outcomes and the optimization of treatment protocols necessitate continued rigorous investigation.

This article provides a narrative review of the current advancements in neuromodulation therapy for PLP, highlighting both the present status and emerging perspectives. It offers valuable insights for clinicians' treatment practices and informs future research by systematically examining the underlying therapeutic mechanisms, clinical applications, and challenges associated with various neuromodulation techniques. Additionally, this review explores potential future directions for the development of neuromodulation therapies, with an emphasis on enhancing treatment efficacy and tailoring individualized PLP management strategies.

2. Mechanisms underlying phantom limb pain

The exact mechanisms underlying PLP remain incompletely understood, but it is widely regarded as a multifactorial pain syndrome involving abnormal sensory, emotional, and cognitive experiences,[7] as well as disturbances in the nervous system.[3] Previous studies have shown that changes in the brain, spinal cord, and peripheral nerves, particularly functional alterations in the primary sensory cortex (S1), primary motor cortex (M1), and thalamus, are directly related to the occurrence of PLP following amputation.[8,9] Evidence suggests that PLP may arise from peripheral input dysfunction and cortical reorganization, as well as abnormal activity in both the peripheral and central nervous systems.[10] It is generally accepted that both the central and peripheral nervous systems play pivotal roles in the initiation and persistence of pain associated with amputation.[11] Overall, most current research highlights the multifaceted nature of PLP's pathophysiology, which involves intricate interactions among psychosocial factors, central nervous system remodeling, and peripheral nerve injury.[1,12] One of the primary challenges in managing PLP lies in addressing the complex interconnections among these processes.

2.1. Peripheral nerve mechanisms

Abnormal nerve fiber regeneration leads to the formation of neuromas, which subsequently increase the release of neuropeptides (such as substance P) and excitatory amino acids (such as glutamate) during the process of peripheral nerve transection-induced structural and functional damage.[8,11] Sodium channels (Nav1.7, Nav1.8) redistribute across the neuroma cell membranes, resulting in aberrant membrane potentials and heightened channel activity, which amplify ectopic discharges and induce abnormal afferent discharge patterns.[13] Following trauma, regenerative sprouting of damaged axons is accompanied by maladaptive structural reorganization, characterized by abnormalities in C-fiber terminal arborization and disorganization of dysmyelinated α-fiber endings (Fig. 1A).[1] This pathological remodeling enhances the transmission of pain signals, with abnormal peripheral neural input serving as a key factor in the induction of PLP.

2.2. Central neural mechanisms

Following injury, neurons may regenerate or sprout into the dorsal horn of the spinal cord,[1] leading to central sensitization,[14] increased excitation of spinal dorsal horn neurons, reduced inhibition, and alterations in the firing patterns of central pain-processing neurons.[10] This results in spinal cord disinhibition and the transmission of nociceptive input to the spinal cord center, thereby intensifying pain signals. At the brain level, cortical remodeling[15,16] and neuroplasticity[17] are key mechanisms. The primary somatosensory and motor cortical areas, once dedicated to the amputated limb, are gradually reorganized to represent adjacent cortical regions.[18] This cortical reorganization leads to the formation of aberrant neuronal connections, which are implicated in both phantom limb sensation and associated pain (Fig. 1B).[19] Furthermore, functional magnetic resonance imaging (fMRI) studies have demonstrated a positive correlation between pain severity and the reorganization of sensory cortical mapping in patients with PLP.[19] Pain processing in spinal circuits is primarily influenced by central sensitization and disinhibition, while alterations in brain regions can modulate pain processing through the regulation of descending pathways.[11]

2.3. Psychological mechanisms

Psychological factors, including emotional responses, cognitive processing, somatic perception, and stress reactions, play a significant role in the onset and progression of PLP (Fig. 1C).[20] Anxiety and depression activate the hypothalamic-pituitary-adrenal axis, leading to the release of cortisol, which exacerbates neuroinflammation and contributes to the development of PLP.[21,22] Catastrophizing pain leads individuals to focus on pain signals, amplifying abnormal cortical activation and perpetuating PLP. Cognitive behavioral therapy, a positive psychological intervention, has been shown to improve neural plasticity, regulate prefrontal cortex function, and enhance the efficacy of neuromodulation therapies.[23] During the management of central pain, psychological stress and emotional factors can alter nervous system responses, potentially worsening or prolonging PLP.[23]

2.4. Mechanism integration and interaction

Peripheral nerve ectopic discharges (peripheral mechanism) can lead to central cortical reorganization (central mechanism), amplifying peripheral pain signals and establishing a "peripheral-central vicious cycle". Psychological factors, such as anxiety, can exacerbate PLP by further promoting central cortical reorganization while simultaneously lowering the pain threshold of peripheral nerves. Neuromodulation therapies can control central reorganization, break the "peripheral-central vicious cycle", and improve the patient's psychological state, thereby creating a multifaceted therapeutic effect. By integrating these three pathways, a "peripheral-central-psychological" three-dimensional model of PLP etiology can be proposed, providing a theoretical framework for discussing Neuromodulation therapy.

3. Neuromodulation in phantom limb pain

Neuromodulation techniques mediate pain relief by directly or indirectly regulating neural circuit functions. The mechanisms underlying PLP involve the reorganization of neural network plasticity, regulatory control over the cortical-spinal-peripheral neural axis,[24] inhibition of abnormal neural signal transmission, and modulation of pain perception.[11,24] Therefore, the primary goal of neuromodulation is to prevent abnormal neuronal discharge patterns while promoting neuronal regeneration and repair processes.[6,7] Neuromodulation techniques can be classified into invasive and non-invasive categories based on their degree of invasiveness. Invasive methods include DBS, SCS, and DRG

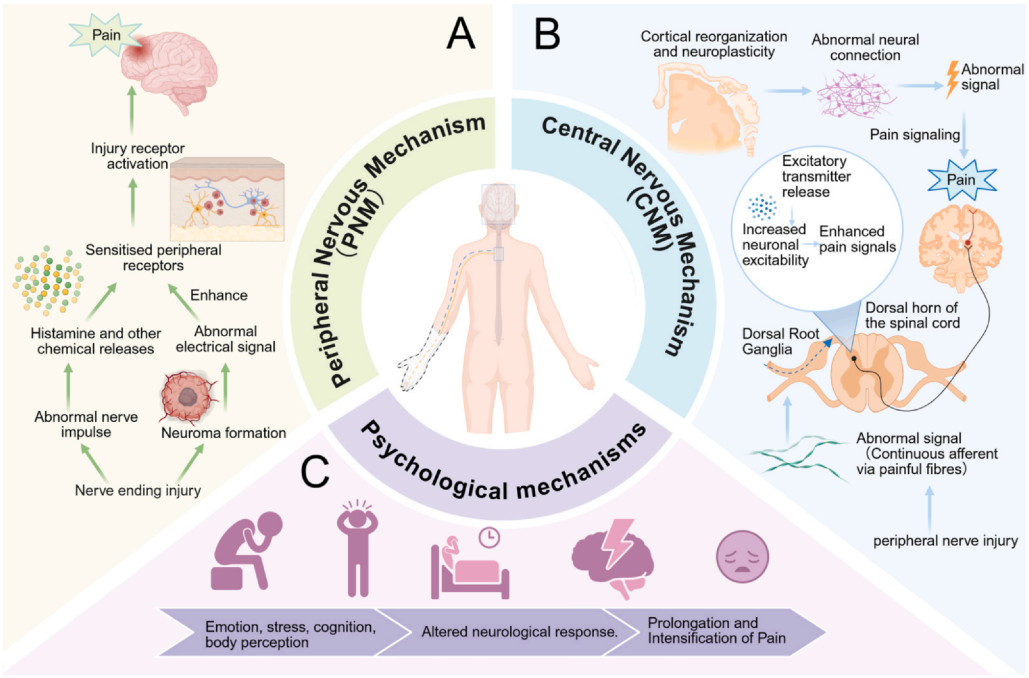

Fig. 1. Mechanisms underlying phantom limb pain. **(A)** Damage to nerve endings causes inflammation or the growth of neuromas, resulting in persistent aberrant discharges and chemical release that exacerbate peripheral sensitization and cause pain. **(B)** Cortical reconfiguration occurs when relevant brain regions replace the lost limb's representation in the sensorimotor cortex following amputation. Changes in neuronal and glial cell plasticity can impact signaling pathways, including ion channels, proteins, neurotransmitters, and metabolites, resulting in aberrant electrical impulses and causing pain. **(C)** Emotional factors impact the incidence and duration of pain following surgery, contributing to Phantom Limb Pain. Abbreviations: PNM, peripheral nervous mechanisms; CNM, central nervous mechanisms.

stimulation.[6] Non-invasive alternatives include TMS, tDCS, and transcutaneous electrical nerve stimulation (TENS).[24]

Neuromodulation represents a promising and innovative treatment strategy for PLP. Numerous studies have demonstrated its potential to significantly alleviate symptoms and enhance patients' quality of life. The following sections provide an overview of the clinical applications of these neuromodulation technologies, as well as a review of the latest advancements in their use for the treatment of PLP.

3.1. Invasive neuromodulation

3.1.1. Deep brain stimulation

DBS involves the implantation of electrodes to deliver electrical stimulation to specific brain regions, thereby modulating the interaction between the brain and spinal cord (Fig. 2A).[25] This technique has demonstrated significant improvements in some PLP patients. For those who do not respond to spinal cord or peripheral nerve stimulation, DBS may serve as an alternative treatment option.[26] DBS alters pain perception by targeting specific brain regions and is widely used in the management of chronic pain.[27] Research indicates that pain relief can be effectively achieved by stimulating various brain areas, including the anterior cingulate cortex (ACC), posterior hypothalamus, internal capsule, periaqueductal gray (PAG), periventricular gray (PVG), and the ventral posterior medial (VPM) and ventral posterior lateral (VPL) nuclei of the thalamus.[27–29] However, the limbic system, which is closely linked to the ACC, as well as networks associated with epilepsy onset, may pose a risk. Neurons in this region are highly excitable and have numerous connections. Electrical stimulation may trigger abnormal synchronous discharges, potentially lowering the threshold for epilepsy onset and inducing epileptic episodes. Thus, careful attention must be paid to avoid these areas in clinical applications.[26,30] Studies have shown that DBS can provide effective analgesia in patients with chronic pain. Although treatment responses vary depending on individual neuropathological characteristics and the selection of therapeutic targets,[31] DBS remains an effective intervention for refractory chronic pain. However, its clinical application faces two primary challenges: significant resource requirements and the potential for surgery-related morbidity. Furthermore, further research is needed to validate long-term efficacy and optimize target selection criteria to establish an evidence-based implementation strategy.

Patients with refractory PLP who do not respond to spinal cord or peripheral nerve stimulation may benefit from DBS. Key targets, such as the thalamus and PAG, have been central to studies demonstrating its effectiveness. However, challenges remain, including high resource demands, increased surgical risks, and unclear target selection criteria. The ACC should be avoided due to the potential risk of epilepsy. Long-term safety and efficacy require validation through large-scale follow-up studies.

3.1.2. Spinal cord stimulation

The primary theory behind the effectiveness of SCS is the gate control theory, which suggests that continuous stimulation of large myelinated fibers in the dorsal column of the spinal cord inhibits pain signals from smaller unmyelinated fibers (Fig. 2B).[25] SCS interferes with electrical and metabolic activities in various brain regions, including the cingulate gyrus, lateral sensory thalamic nucleus, prefrontal cortex, and postcentral gyrus, thereby producing analgesic effects.[32] Additionally, distinct opioid receptor types are activated by different SCS frequencies, contributing to pain relief.[33] SCS has become one of the most important treatments for PLP due to its reversibility and minimal invasiveness. Research shows that SCS can alleviate PLP with long-term success rates ranging from 14% to 80%, although its effectiveness may decrease over time.[34] Variations in success rates are influenced by technical factors (e.g., stimulation frequency, pulse width, voltage, and electrode placement), patient characteristics (e.g., duration of PLP, pain type, and comorbidities), and follow-up periods. While immediate therapeutic benefits are often significant, long-term relief may be less consistent.[35–37] Possible mechanisms of analgesic tolerance include reduced endorphin secretion, increased release of excitatory amino acids (such as glutamate), desensitization of opioid receptors, and insufficient reversal of abnormal cortical reorganization following prolonged stimulation, which can lead to pain recurrence.[38] Despite its popularity as a minimally invasive and reversible procedure for PLP, SCS is associated with challenges such as analgesic tolerance and variable long-term success rates. Key issues that need further resolution include the standardization of treatment parameters and ensuring the durability of therapeutic effects.

3.1.3. Dorsal root ganglion stimulation

DRG neuromodulation, as a complement to SCS, is increasingly being applied in clinical practice. By directly targeting and repairing damaged neurons in the DRG, it inhibits overactive neuron populations,

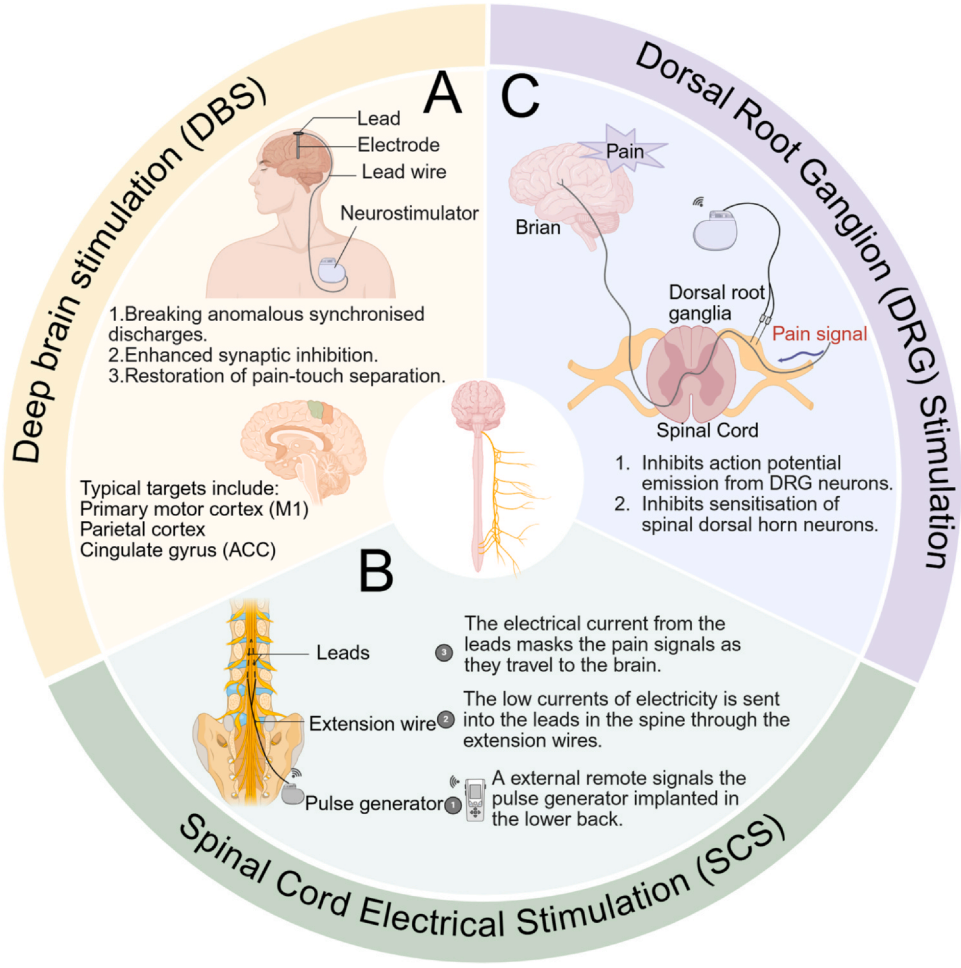

Fig. 2. Overview of the mode of action of invasive neuromodulation. **(A)** Rebuilding of neural circuits using electrical stimulation signals to modify neuronal activity in the target region. **(B)** Inhibiting pain signaling by employing electrical stimulation signals to activate inhibitory neurons in the spinal cord's dorsal horn. **(C)** Electrical stimulation signals inhibit aberrant discharge in dorsal root ganglion neurons, thereby decreasing the transmission of pain signals to the central nervous system. Abbreviations: ACC, anterior cingulate cortex; DBS, deep brain stimulation; DRG, dorsal root ganglion; M1, primary motor cortex; SCS, spinal cord stimulation.

producing analgesic effects (Fig. 2C).[39,40] Studies have shown that the occurrence of PLP is closely linked to primary sensory neurons in the DRG, and stimulating the DRG can disrupt symptom correlation.[41,42] Notably, patients report high satisfaction rates with both SCS and DRG electrical stimulation. These therapies are typically considered second-line treatment options after the failure of drug therapy, particularly for chronic refractory pain phenotypes.[43] A case study involving patients who underwent right upper limb amputation demonstrated the feasibility of this approach. After insufficient results from drug intervention, SCS provided pain relief and reduced the need for analgesic medications. However, longitudinal follow-up revealed the progressive recurrence of symptoms and the necessity for adjunctive medication for symptom management.[37] Comparative analyses indicate that DRG stimulation offers more precise coverage of segmental sensory abnormalities, addressing the issue of sensory abnormality spread commonly seen with SCS. Additionally, DRG stimulation provides superior stability, long-term effectiveness, and a higher rate of pain alleviation.[44–46]

DRG stimulation offers substantial benefits in conjunction with SCS in terms of electrode reliability, long-term effectiveness, and accurate coverage of sensory anomalies. This is appropriate for PLP patients with limited pain segmentation or weak SCS efficacy. However, long-term safety still needs to be demonstrated in large-scale, expensive studies.

3.2. Non-invasive neuromodulation

3.2.1. Transcranial direct current stimulation

tDCS is a non-invasive neuromodulation technique that has gained considerable attention in recent years within the neuroscience community. The basic principle involves applying a low current (1–2 mA) to specific scalp areas, modulating the membrane potential of neurons without directly triggering action potentials.[25] The primary mechanism of tDCS is the alteration of the resting membrane potential, which subsequently influences neuronal excitability and the resulting neural activity patterns (Fig. 3A).[48] The M1 and cerebellum are key sites in tDCS research for treating PLP.[49] Due to its simplicity, potential therapeutic benefits, and non-invasive nature, tDCS holds promise for modulating brain function and enhancing cognition and behavior.[50] tDCS has shown significant effectiveness in treating chronic neuropathic pain, particularly PLP, which is often complex and resistant to treatment. Bolognese et al. conducted a two-week, double-blind, crossover trial to examine the analgesic effects of tDCS on M1. The results demonstrated that a 5-day course of M1 stimulation with tDCS could provide stable relief from PLP in chronic amputee patients.[51]

tDCS alleviates PLP symptoms through the neural plasticity adaptation mechanism of M1.[50] This neuroregulatory effect not only supports tDCS as a viable intervention for neuropathic pain but also clarifies the neurophysiological factors involved in the pathogenesis of PLP. When combined with multimodal rehabilitation programs, therapeutic outcomes can be enhanced. Specifically, when paired with mirror therapy (MT), tDCS demonstrates a synergistic effect in treating PLP.[52–54] Segal et al.[55] conducted a three-arm randomized controlled trial with 30 participants, who were divided into three groups: MT alone, MT combined with pseudo-tDCS, and MT combined with true tDCS. The results showed that during the 3-month follow-up, pain reduction in the combined intervention group was more significant than in the two control groups. These findings suggest that tDCS combined with MT offers long-term therapeutic benefits, providing a sustained analgesic strategy for PLP patients. As an advanced neural regulation

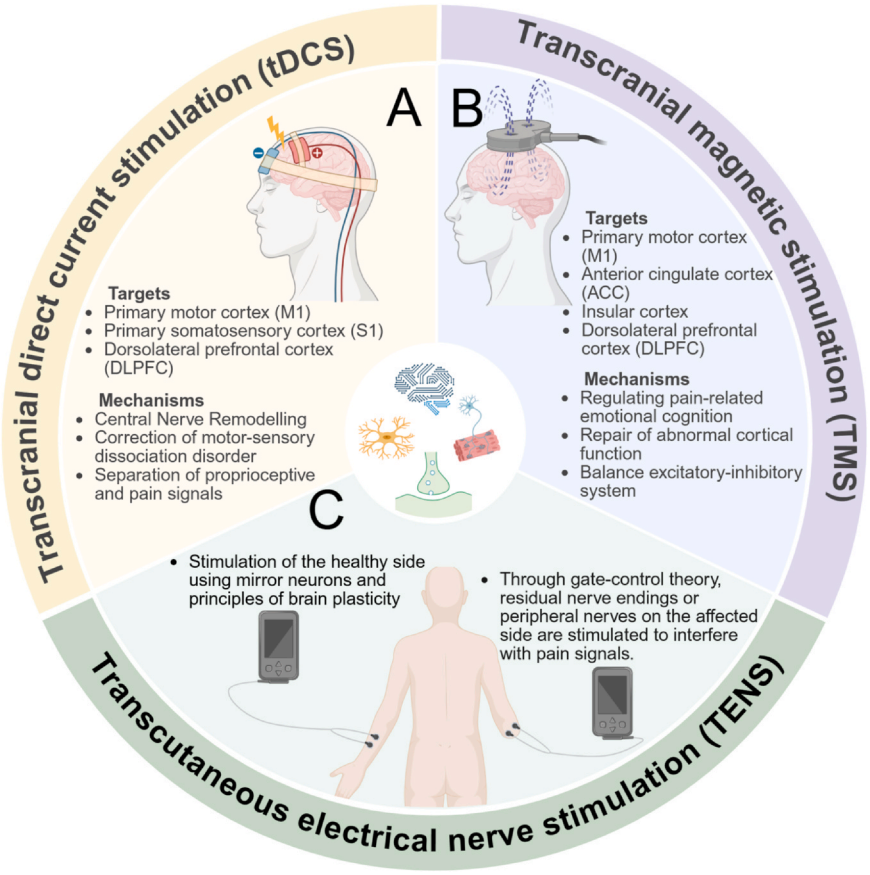

Fig. 3. Overview of the mode of action of non-invasive neuromodulation. **(A)** The mechanisms of action are linked to central nervous system plasticity and remodeling/dysfunction in brain regions, particularly in the abnormal sensory cortex mapping and hyperactivation of the limbic system associated with phantom limb pain. **(B)** Repair of central nervous system remodeling and malfunctioning brain regions associated with pain, leading to the reconstruction of the neural network. **(C)** Activation of Aβ fibers in the corresponding innervated area of the phantom limb via electrical stimulation signals to re-establish the spinal cord's gated inhibitory pathway, as described by the 'gate-control theory'[47]. Abbreviations: S1, primary somatosensory cortex; DLPFC, dorsolateral prefrontal cortex; TENS, transcutaneous electrical nerve stimulation; TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

model, the collaborative application of tDCS and MT holds significant potential for treating refractory neuropathic pain. To further elucidate central pain-processing mechanisms and optimize PLP treatment frameworks, future research should focus on large-scale randomized controlled trials and integrate tDCS with brain imaging techniques such as fMRI and quantitative electroencephalography (EEG) to establish neurophysiological predictors of treatment responsiveness.[56]

The benefits of tDCS include its non-invasiveness, safety, and ease of use. Stimulation of the cerebellum or M1 has been shown to effectively reduce PLP, and when combined with mirror therapy, it enhances therapeutic efficacy and prolongs analgesic effects. However, drawbacks include the lack of standardized stimulation parameters and considerable individual variation in treatment outcomes. Additionally, obtaining data on long-term effectiveness remains challenging.

3.2.2. *Transcranial magnetic stimulation*

TMS is a widely used non-invasive neurophysiological technique for assessing cerebral cortex function. It involves the application of electromagnetic pulses to stimulate the cerebral cortex, thereby modulating neural activity (Fig. 3B).[25] Repetitive transcranial magnetic stimulation (rTMS) has been employed in clinical settings to treat depression for nearly 20 years,[57] though further research is needed to optimize stimulation frequency and intensity for maximum benefit. In one study, 1 Hz rTMS was used to activate the contralateral cortical motor area in patients who had undergone left arm and right foot amputations. The results showed a reduction in visual analog scale (VAS) scores in patients with left arm amputations, but no significant change in those with right foot amputations.[58,59] In another study, 54 patients with PLP following landmine injuries received 10 Hz rTMS stimulation at 90% resting motor threshold (RMT). Compared to the sham stimulation group, the experimental group reported significantly less discomfort after treatment.[60] A study involving 17 PLP patients who received 20 Hz rTMS stimulation to the hand region of M1 in their healthy limb found that patients with upper extremity amputations experienced better pain relief than those with lower extremity amputations. The therapeutic application of rTMS resulted in a 55% reduction in VAS scores by the end of the treatment, a decrease that was superior to the control group.[61] Several studies indicate that stimulating the contralateral parietal cortex produces transient analgesic effects, while targeting the unaffected hemisphere with low-frequency rTMS or applying high-frequency rTMS to the contralateral M1 can significantly alleviate PLP.[58,62,63]

Emerging evidence suggests that the dorsolateral prefrontal cortex (DLPFC) plays a role in harmful top-down regulation and may mediate analgesia by inhibiting the thalamic-cingulate loop. The modulation of DLPFC connections with pain-related brain regions, including the amygdala, ACC, and cingulate cortex, is crucial for exerting an analgesic effect.[64] These neuroanatomical findings provide new insights into the selection of PLP treatment targets. Although rTMS is a non-invasive treatment method, significant knowledge gaps remain regarding neural regulatory mechanisms, targeting accuracy, and parameter optimization. Methodological standardization through large-scale multicenter trials is essential to establish evidence-based treatment protocols.

PLP can be effectively and non-invasively treated with rTMS. Key targets, such as the DLPFC and contralateral M1, demonstrate significant analgesic effects in both the short- and long-term, with sustained efficacy. However, challenges remain due to inconsistent settings and insufficient targeting accuracy. Large-scale multicenter trials are needed to confirm the evidence.

3.2.3. *Transcutaneous electrical nerve stimulation*

TENS provides non-invasive analgesia by applying an electric current to the skin surface, thereby modulating both central and peripheral nerve pathways (Fig. 3C).[65] The therapeutic mechanism involves the activation of the endogenous neuroregulatory system, including opioid

receptors in the brainstem and the 5-hydroxytryptaminergic/dopaminergic receptor network in the spinal cord.[66] The effectiveness of TENS is directly influenced by parameters such as stimulation frequency, pulse width, current intensity, and waveform configuration. Based on these parameters, TENS can be classified into different types: normal TENS, acupuncture-like TENS, burst-mode TENS, and brief intense TENS.[67,68] For chronic neuropathic pain management, including PLP intervention, traditional TENS with high frequency, short pulse, and low intensity is primarily used.[69,70] Clinical trials have shown that combining TENS with MT enhances therapeutic outcomes and is more effective than MT monotherapy in alleviating PLP symptoms.[71]

The precision of electrode placement is crucial for treatment success. Different electrode placements—on the same or opposite sides—affect the activation of the endogenous opioid system. Electrode placement on the affected limb and corresponding body surface sensory area activates endorphin release in the posterior horn of the spinal cord on the same side, blocking the transmission of peripheral pain signals to the central nervous system. Conversely, placing the electrodes on the opposite side of the corresponding body surface sensory area on the healthy side activates the endogenous opioid system via a cross-inhibitory mechanism, providing indirect pain relief on the affected side.[72] When electrodes are placed accurately, TENS can significantly reduce pain intensity and potentially promote sensory feedback to the phantom limb, aiding perceptual integration with the prosthetic limb.[73] Stimulation of the contralateral side of the amputee limb, corresponding to the PLP position, can provide prolonged analgesia after two treatment courses.[74,75]

Empirical evidence suggests that both low-frequency modulated and constant-frequency TENS protocols elevate nociceptive thresholds, requiring suprasensory but subharmful current density parameters for optimal therapeutic efficacy.[76] Mechanistic studies have shown that pulse-width-modulated (PWM) TENS-induced corticomotor reorganization and corticospinal pathway potentiation are neuroplastic correlates of PLP remission.[77,78] These neuroplastic changes validate PWM-TENS as a viable neuromodulation strategy for PLP management. To maximize TENS's therapeutic potential, future research should focus on exploring the effects of different TENS types in specific pain management regimens, optimizing electrode placement and parameter settings, and developing hybrid neuromodulation regimens that combine TENS with MT[71] and other neurorehabilitation methods.

TENS offers several benefits, including low cost, ease of use, and non-invasiveness. Its therapeutic effects may be enhanced when combined with mirror therapy. Placing the electrodes on the same side of the body yielded more favorable results than placing them on the opposite side. However, the analgesic effects are generally transient, and the therapeutic benefits are not sufficiently long-lasting. Two key areas for future optimization are the refinement of treatment parameters and the standardization of electrode placement.

4. Novel neuromodulation approaches

Emerging neuromodulation paradigms show significant translational potential for PLP management, despite current focus on alternative pain etiologies. Although contemporary research has primarily concentrated on non-PLP neuropathic pain syndromes, growing preclinical evidence supports the therapeutic potential of innovative neuroregulatory approaches for addressing phantom limb pathophysiology. However, these technologies are mostly in the preclinical or early clinical stages, lack sufficient clinical validation, and remain clearly distinguishable from established evidence-based therapies such as SCS and rTMS.

4.1. Brain-computer interface (BCI)

The BCI establishes a direct connection between the brain and external devices by decoding brain activity signals and converting them into effector control signals (Fig. 4A).[15,79] This neurorehabilitation model enhances sensorimotor integration in individuals with limb loss by reshaping maladaptive neural circuits and regulating cortical excitability.[80] BCI enables neural training for virtual limb perception, helping patients restore the ability to perceive phantom limbs and alleviate associated discomfort.[81] Neurocognitive rehabilitation strategies that use healthy limb movement visualization to enhance cortical representation have shown promise in helping patients control phantom limb sensations, normalizing signal processing in abnormally missing limbs and thereby reducing the symptom burden of PLP.[81,82] Technologies that recognize muscle electrical patterns can be incorporated into BCI systems to control virtual reality, facilitating virtual limb movement by deciphering muscle electrical signals. This improves sensorymotor integration and reduces PLP.[83,84] Future therapeutic innovations may arise from multimodal integration with BCI architectures such as EEG, magnetoencephalography (MEG), and fMRI, in collaboration with virtual reality platforms and MT solutions. This integration is expected to develop an intervention framework that is time-precise, neuro-malleable, and optimized for PLP management.[3]

4.2. Temporally interfering stimulation (TIS)

TIS is an innovative neural stimulation technique that enhances neuronal excitability by temporally modulating current waveforms. It uses two high-frequency sinusoidal currents with a minimal frequency difference to generate low-frequency envelope oscillations in deep brain targets, selectively activating deep brain structures (Fig. 4B).[85] TIS can penetrate as deep as 2–3 cm, providing superior depth compared to standard tDCS, and is more effective than conventional tDCS in targeting subcortical areas such as the hippocampus.[86,87] A key advantage of TIS is its ability to regulate neurons at different depths within brain tissue while preserving the integrity of the surface cortex. This characteristic makes TIS a promising approach for treating certain neuropsychiatric disorders.[88] Preclinical studies using multi-channel transcranial temporal coherent electrical stimulation in mouse models have shown that reducing the stimulation intensity of the multi-channel setup enhances neuronal activation selectivity, indicating that expanding the electrode array improves stimulation focus while minimizing scalp sensations.[89] Violante I.R. et al.[90] conducted a single-blind crossover study on incremental current titration (0.1 mA to 0.45 mA/cm^2); the stimulation groups were exposed to currents at frequencies of 2.005 and 2 kHz, demonstrating that excitability modulation in the hippocampus is linked to memory enhancement. Emerging clinical evidence further supports the therapeutic potential of TIS, showing efficacy in drug-resistant epilepsy models.[91,92] TIS is expected to be explored as a treatment for PLP, offering a novel approach to address neuropsychiatric disorders and pain management. With these mechanistic insights and technical advantages, TIS is a promising candidate for PLP intervention research, establishing a new neuro-engineering framework for managing chronic neuropathic pain.

4.3. Transcranial focused ultrasound (tFUS)

tFUS uses focused ultrasonic waves to target specific brain regions (Fig. 4C). Its advantages include high spatial resolution, deep penetration, and non-invasiveness.[93] Low-intensity FUS pulses stimulate or inhibit neurons and other excitable cells.[94] While tFUS has shown potential for neurotherapy in conditions such as epilepsy, neuropathic pain, Alzheimer's disease, and Parkinson's disease,[95–99] no clinical studies have yet explored its application in PLP treatment. Research indicates that different tFUS stimulation methods can modulate cortical excitability effectively.[100] A study on M1 modulation via tFUS revealed that varying tFUS parameters can produce both excitatory and inhibitory effects. By altering the excitation-inhibition balance associated with GABAergic and glutamatergic receptor activities, as well as neurotransmitter metabolism, tFUS can influence cortical excitability and

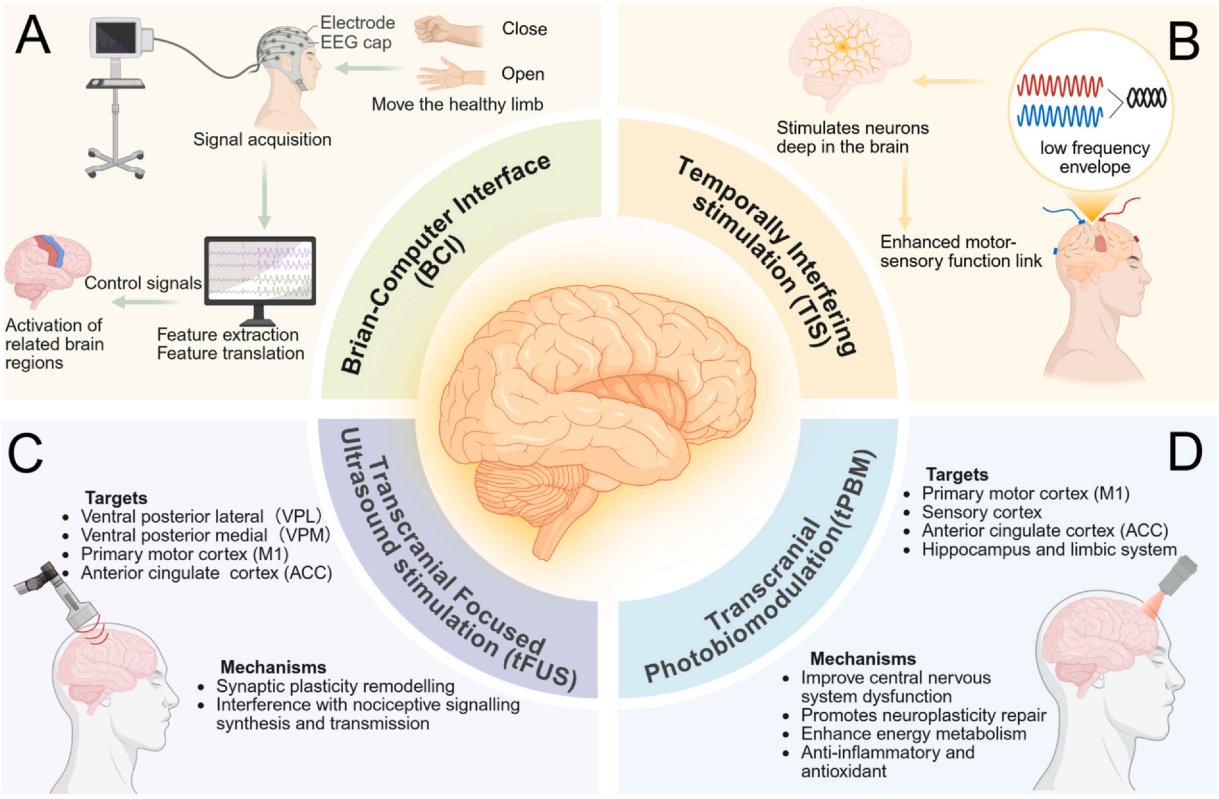

Fig. 4. Overview of the modes of action of novel neuromodulation approaches. **(A)** Through real-time feedback training of brain-computer interface, sensory inputs can be rebuilt, and abnormal cortical discharges can be inhibited, consequently repairing the 'motor-sensory dissociation', and ultimately correcting the brain's incorrect representation of the missing limb. **(B)** By combining neuromodulation principles with plasticity remodeling, TIS can repair the spatiotemporal aberrations in neural circuits associated with phantom limb pain by synchronizing sensory and motor activities in the brain. **(C)** Following the application of ultrasound energy, central neural circuits can be accurately regulated, thereby reversing neuroplastic changes and facilitating repair. **(D)** Through light stimulation, neuronal activity is enhanced, dysfunction of the central nervous system is improved, and the repair of neural plasticity is promoted. Abbreviations: VPL, ventral posterior lateral; VPM, ventral posterior medial; BCI, brain-computer interface ; EEG, electroencephalography; TIS: temporally interfering stimulation; tFUS, transcranial focused ultrasound; tPBM, transcranial photobiomodulation.

plasticity.[101] Given its potential to modulate cortical and deep brain nuclei activity, tFUS is considered a promising neuromodulation tool in conjunction with PLP treatment mechanisms.

4.4. Transcranial photobiomodulation (tPBM)

tPBM is a newly developed treatment method that directly exposes the cerebral cortex to low-intensity light sources, such as red or near-infrared light, to enhance cerebral hemodynamics, neural regeneration, and brain metabolism (Fig. 4D).[102,103] tPBM operates through multiple mechanisms, including the enhancement of cellular energy production, improvement of blood flow and oxygen supply, modulation of synaptic plasticity, and reduction of oxidative stress.[103] It boasts a high safety profile and can be used in various settings, including non-invasive real-time quantification of its effects on the brain using MRI.[104] Although tPBM has shown considerable promise in neural regeneration and functional recovery following spinal cord injury, as well as in treating central nervous system disorders such as stroke,[105] cognitive disorders,[106] Alzheimer's disease,[107] aphasia,[108] and traumatic brain injury,[109] its specific application and therapeutic effects in PLP treatment require further research and clinical trials. With continued investigation into PLP, tPBM may emerge as a viable therapy for managing the condition.

New approaches to treating PLP have been enabled by neuromodulation technologies such as BCI, TIS, tFUS, and tPBM. These methods offer precision and minimally invasive (or non-invasive) options with significant potential benefits. However, most relevant studies lack large-sample clinical evidence specific to PLP and remain in the preclinical or early clinical stages. Additionally, the associated costs are substantial, and clinical translation remains challenging. Long-term safety validation and clinical implementation are key priorities for future research.

5. Current challenges and prospects

While neuromodulation technologies hold significant potential for treating PLP, they still face substantial challenges. The primary issue is the significant variability in treatment response among patients, which arises from differences in neurophysiological characteristics, etiological and pathological factors, and phenotypic pain expression patterns. These factors all influence treatment outcomes.[7] The uncertainty surrounding the pathogenesis of PLP and the duration of pain further complicates treatment.[110] Existing treatment models struggle to accommodate the diversity of PLP, emphasizing the need for personalized treatment approaches. Variability in therapeutic outcomes across different stimulation protocols remains considerable, and there are no standardized guidelines for DBS, TMS, or SCS parameter settings. Recent research has largely focused on developing treatment plans tailored to individual patient needs to optimize outcomes. Longitudinal safety and efficacy validation represent another critical frontier, given the transient nature of current therapeutic approaches and the risks of iatrogenic complications, such as device-related infections and hardware failures. A further challenge for the widespread application of neuromodulation therapy is its high cost and complex operational procedures, particularly in resource-limited settings where specialized neuromodulation infrastructure is lacking.

A current priority is to identify research gaps and establish clear directions for future studies. Researchers should focus primarily on optimizing existing technologies, such as standardizing neural regulation parameters, improving electrode stability, and extending the duration of therapeutic efficacy. Secondly, developing combined treatment approaches, such as tDCS with mirror therapy or SCS with medication, should be prioritized. Long-term research goals include developing personalized treatment regimens, conducting safety and efficacy studies of key technologies over extended periods ($\geq$5 years), and advancing clinical translation research for emerging technologies.

To strengthen the link between mechanisms and treatments, rTMS and tDCS can be utilized to regulate cortical functions involved in central cortical reorganization. Cognitive behavioral therapy and neural regulation therapies can be integrated to address psychological factors, while SCS and DRG stimulation may be employed to inhibit peripheral pain signal transmission, targeting the mechanism of ectopic discharge in peripheral nerves.

Despite these challenges, neuromodulation, as a novel intervention model, shows considerable promise for treating PLP. Driven by advancements in neurotechnology, emerging models such as BCI, TIS, tFUS, and tPBM are progressing from preclinical validation to clinical trials. These techniques offer precise neural regulation, enhanced spatial resolution, and reduced invasiveness, making them viable alternatives for refractory PLP. Although current evidence largely stems from studies on non-PLP chronic pain, the increasing similarities in underlying mechanisms support the rationale for researching PLP.

The technological convergence of artificial intelligence (AI) and big data analytics has ushered in a new era of personalized neuromodulation. The integration of clinical phenotyping, neuroimaging biomarkers, and genomic profiling enables the development of patient-tailored therapeutic strategies.[111] Enhanced targeting accuracy, coupled with closed-loop parameter optimization, has the potential to provide sustained therapeutic benefits, expanding non-invasive treatment options for PLP patients. However, to fully realize this potential, further basic research, large-scale clinical trials, and technological innovations are essential. These efforts will be key to overcoming current limitations and facilitating the broader clinical application of neuromodulation techniques in PLP.

6. Limitations

This narrative review has several limitations: (1) Potential publication bias: The majority of the included studies reported favorable outcomes, which may introduce publication bias and affect the neutrality of the evidence; (2) Quality of included studies: The credibility of the evidence is limited by the small sample sizes, short follow-up durations, and lack of long-term efficacy data in some studies; (3) Literature gaps: Key technologies, such as DRG stimulation, lack long-term safety data ($\geq$5 years), and emerging technologies have no clinical conversion evidence; (4) Specific limitations: This review did not examine the combined effects of multiple neuromodulation therapies, did not include a meta-analysis, and lacked sufficiently precise quantitative comparisons of the effectiveness of each therapy.

7. Conclusion

Neuromodulation therapies offer significant therapeutic potential for treating PLP, improving patient quality of life, and alleviating clinically significant pain. The primary contributions of this study are as follows: it integrates the peripheral, cerebral, and psychological mechanisms of PLP and explains how these mechanisms interact; it systematically compares the effectiveness, benefits, and drawbacks of invasive (DBS, SCS, DRG stimulation) and non-invasive (tDCS, rTMS, TENS) neural regulation therapies; it expands on emerging neural regulation technologies and highlights how they differ from evidence-based therapies; and it proposes clinical treatment options and future research priorities. Key findings include: evidence-based platforms support technologies such as SCS, DRG stimulation, rTMS, and tDCS. SCS is less effective than DRG stimulation in terms of long-term persistence. The combination of mirror therapy, rTMS, and tDCS enhances therapeutic efficacy. However, clinical translation requires further development, and new technologies are still in the investigative stage.

Persistent challenges remain in four critical areas: (1) inter-patient neurobiological heterogeneity, (2) stimulation parameter optimization, (3) longitudinal safety and efficacy validation, and (4) cost-effectiveness barriers in clinical translation. Prospective developments in neuromodulation are poised to advance toward personalized precision therapeutics through technological convergence. Emerging paradigms such as BCI, TIS, tFUS, and tPBM leverage enhanced spatial resolution and non-invasive delivery to address the pathophysiological complexity of PLP. The synergy between big data analysis and AI has further optimized patient-specific treatment regimens. Next-generation neuromodulation technologies may offer continuous, cost-effective treatment outcomes, ultimately redefining the standard care model for the PLP population.

CRediT authorship contribution statement

Jingming Hou: Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Rubing Yan:** Resources, Project administration. **Han Chen:** Project administration, Methodology. **Zhou Feng:** Visualization, Software, Methodology. **Peng Tang:** Writing – review & editing. **Lijuan Xie:** Writing – review & editing. **Xiaoyan Duan:** Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Data curation. All the authors have read and approved the final version of this manuscript.

Ethics approval

Not applicable.

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Data Availability

Not applicable.

Declaration of Competing Interest

Jingming Hou is an editorial board member of Healthcare and Rehabilitation but has not been involved in the journal's review or decisions related to this manuscript. The authors declare that they have no known competing financial interests or personal relationships related to this work.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this study, the authors used ChatGPT-4 and DeepSeek (latest version) to optimize the language expression and improve the readability of the manuscript. All content generated by these AI tools was carefully reviewed, revised, and verified by the authors. The authors take full responsibility for the scientific content, accuracy, and integrity of the final published article.

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