Science Bulletin xxx (xxxx) xxx

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Perspective

The dual role of electrical stimulation in pain: from management to reconstruction

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Pain is a common sensory experience in our daily lives. Persistent or recurrent pain affects over 30% of the global population, imposing a significant burden on individuals and society. Nevertheless, normal pain perception functions as a warning mechanism for the body and is essential for survival. The propagation of electrical signals is central to pain perception, and the capacity to modulate these signals is crucial for human pain regulation. Currently, the applications for electrical stimulation in pain management are gradually expanding, offering patients innovative treatment options. Additionally, advancements in bionics have led to increased attention on reconstructing pain perception through artificial synapses, electronic skin, and prosthetics. Here, we focus on the dual role of electrical stimulation in both pain management and pain reconstruction, highlighting their shared developmental trends.

Advancements in electrical stimulation for pain management. Despite the prevalent use of pharmacological interventions for pain management, the inappropriate use of these medications has precipitated a marked increase in severe addiction. Electrical stimulation represents one of the most successful alternative methods, providing a viable option for alleviating various refractory pain conditions. Electrical stimulation has been used for pain management began in 1967 based on Melzack and Wall's gate control theory. Under the premise that the stimulation of fast-velocity mechanoreceptive Aβ fibers can prevent slower moving nociceptive signals transmitted by Aδ and C fibers from reaching higher centers of the brain and leading to pain relief, electrical stimulation has flourished in the field of analgesia. Fig. 1a outlines the historical development and classification of electrical stimulation for pain management. Electrical stimulation typically classified into invasive and non-invasive methods (Fig. 1b). These electrical stimulation technologies have demonstrated their clinical value. As an example, spinal cord stimulation (SCS) for chronic pain is experiencing exponential growth. Over 270,000 patients worldwide have benefited from SCS, and the market for this therapy is estimated to be worth $2 billion annually. With the accumulation of clinical evidence, the scope of electrical stimulation in pain management continues to expand (Fig. 1b). In clinical practice, electrical stimulation devices have undergone further technological improvements. Advancements such as wireless communication and closed-loop control systems have been initially explored and applied in the field of pain management. For example, Nalu™ Neurostimulation System (Nalu Medical, CA, USA) was designed for spinal cord stimulation to treat chronic pain conditions. This system was powered by an external battery (Therapy Disc), which houses a rechargeable lithium-ion battery and electronics. The Therapy Disc can wirelessly power the implantable pulse generator using inductively coupled radiofrequency energy.

In recent years, the paradigm of electrical stimulation for pain management is anticipated to shift beyond traditional frameworks and move towards the direction of "bioelectronic drug" (Fig. 1b). This shift is fueled by advancements in materials and microelectronics, which offer unprecedented opportunities for miniaturizing electrical stimulation devices and enabling minimally invasive surgery. A notable development is the advent of macroporous flexible mesh electronics, which can be injected into biological tissues using a syringe. Once injected, these electronics conform to the internal spaces of tissues, offering a less invasive method for pain management [1]. Additionally, the field has seen the emergence

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https://doi.org/10.1016/j.scib.2025.01.052

Please cite this article as: K. Xu, Y. Ma, T. Ye et al., The dual role of electrical stimulation in pain: from management to reconstruction, Science Bulletin, https://doi.org/10.1016/j.scib.2025.01.052

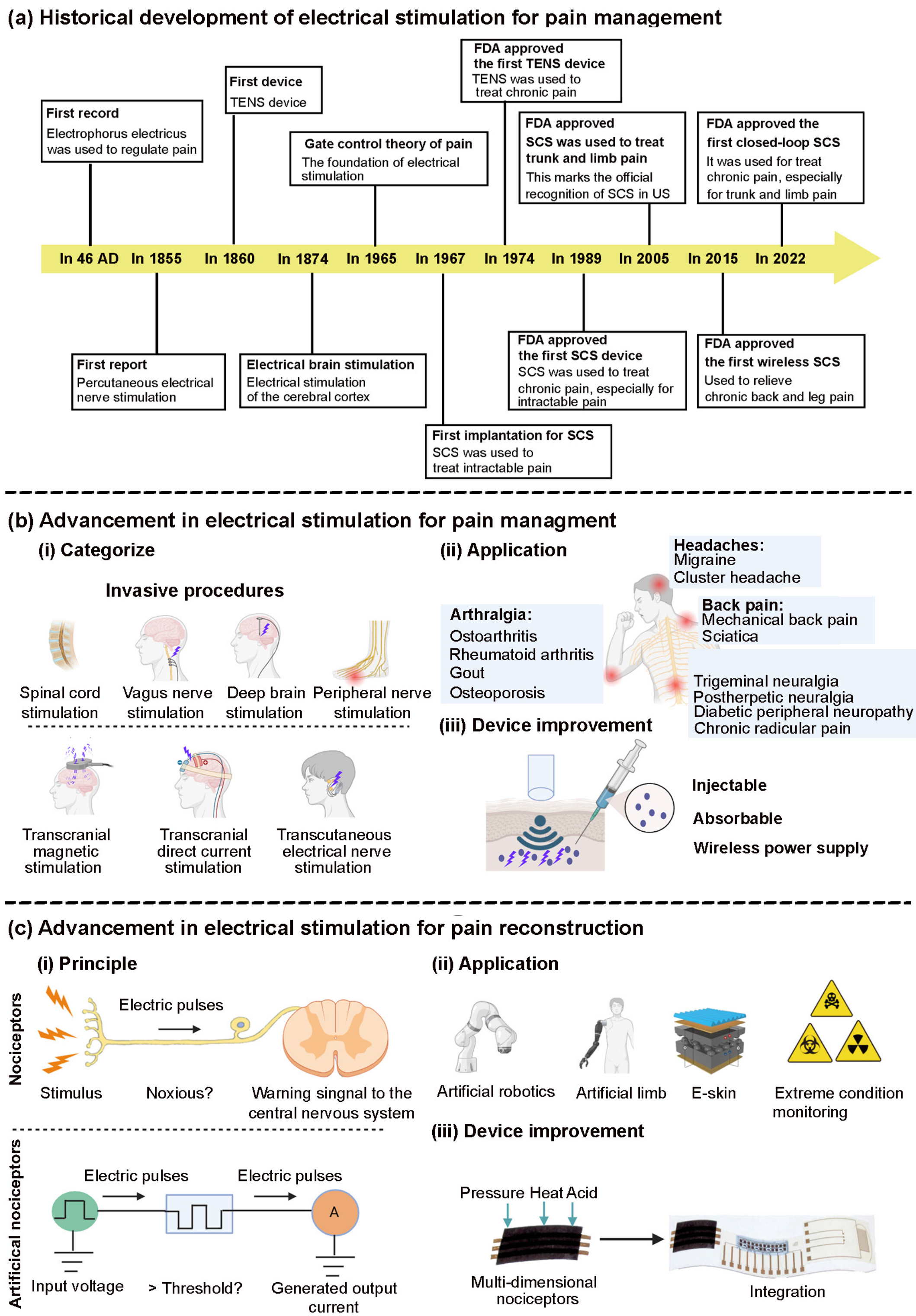

Fig. 1. Advancements of electrical stimulation in pain management and reconstruction. (a) Historical development of electrical stimulation for pain management. (b) Advancements in electrical stimulation for pain management: (i) Invasive and non-invasive methods of electrical stimulation for pain management; (ii) Indications for pain management through electrical stimulation; (iii) The development direction of electrical stimulation devices for pain management. (c) Advancements in electrical stimulation for pain reconstruction: (i) Artificial nociceptors simulate the perception of nociceptive stimuli; (ii) Applications of electrical stimulation in pain reconstruction; (iii) The development direction of artificial nociceptors in pain management. Panels (b) and (c) were created with Biorender.com.

of conductive hydrogels and functional nanoparticles, which can be shaped and delivered within the body, providing a safer and more adaptable approach to electrical stimulation. For example, injectable magnetoelectric nanoparticles and piezoelectric nanoparticles exhibit exceptional magnetoelectric and piezoelectric properties, enabling them to generate significant electrical currents when exposed to external magnetic fields and ultrasound, respectively. These injectable electronic devices can function like standard electronic devices within tissues, potentially unlocking a novel application for the pain management through electrical stimulation.

The development of flexible and absorbable electrical stimulators provides new opportunities for pain management by electrical stimulation. For example, a bioabsorbable nerve stimulator was developed for acute pain [2]. The electrodes and electrical interconnect traces rely on bioresorbable metals, including molybdenum and magnesium, while the encapsulation materials and support substrates are derived from bioabsorbable polymers. Studies in live animal models demonstrated successful pain relief through peripheral nerve stimulation during the 9-day implantation period, with almost complete degradation after 2 months. The development of biodegradable piezoelectric hydrogels for osteoarthritis treatment also marks a significant step forward in minimally invasive pain management [3]. The bioresorbable nature of these bioelectronic devices mitigates the risks associated with secondary surgeries for device removal, with potential to replace or complement conventional electrical stimulation approaches.

Supplying power to implantable devices is still a technical challenge for pain management through electrical stimulation. Recently, a novel implantable piezoelectric ultrasound energy-harvesting device based on Smdoped $Pb(Mg_{1/3}Nb_{2/3})O_3$-$PbTiO_3$ single crystal was developed with the output power density up to 1.1 W/cm^2 *in vitro* [4]. Electrophysiological experiments demonstrate that this wireless-powered device is well qualified for analgesia applications through activating the periaqueductal gray brain area. Additionally, there have been innovations in the development of micro/nanoparticle systems that can convert various forms of energy into electrical power. These systems offer new possibilities for the development of electrical stimulation devices. For instance, advances in triboelectric nanogenerators have shown potential for harnessing mechanical energy from the human body for powering implantable devices.

These studies have facilitated the advancement of electrical stimulation in pain management, achieving its injectable, absorbable, and completely wireless power supply. Future research orientations might involve the utilization of stimulus–response materials to trigger the degradation of bioelectronic devices, attaining precise control of injected or implanted devices at the single-cell level, and developing integrated two-way wireless communication modalities for closed-loop system control. With the ongoing advancement of material science and artificial intelligence technology, the application of electrical stimulation in pain management will break through the traditional paradigm and develop in the direction of being more convenient, more effective, and more intelligent.

Advancements in electrical stimulation for pain reconstruction. Although persistent or recurrent pain imposes a significant burden, normal pain perception is an essential warning mechanism for survival. Pain reconstruction refers to the process of artificially replicating the sensory experience of pain by converting abnormal external stimulation into electrical stimulation [5]. During pain perception, when a noxious stimulus is received from a free nerve ending, the nociceptor compares the amplitude of the signal with a threshold value and decides whether an action potential should be generated and sent to the brain via the spinal cord (central nervous system). To simulate the process of pain perception, pain reconstruction commonly utilizes sensors to transform external stimuli into electrical signals. When the pulse amplitude is higher than the threshold voltage of the artificial nociceptors, the device is turned on, and current pulses are generated (Fig. 1c). This approach focuses on the creation of artificial nociceptors that can encode electrochemical signals, injecting new vitality into the fields of intelligent robotics, artificial limbs, electronic skin and extreme environment monitoring (Fig. 1c).

Biological nociceptors possess four vital properties: threshold, no adaptation, relaxation, and sensitization. Currently, researchers have identified two primary strategies to replicate the complex functions of nociceptors. One common strategy is to combine sensors and synaptic-like devices. These sensors convert external mechanical, thermal, or chemical signals into electrical signals, which are then processed by a memristor or a transistor. For example, to mimic the behavior of Aδ fibers (fast pain) and C nerve fibers (slow pain) in nociceptive transmission, an artificial pain-perceptual system was fabricated via the heterogeneous integration of two retention-differentiated memristors and a piezoresistive pressure sensor [6]. In this system, memristors of varying thicknesses represent the Aδ and C nerve fibers of nociceptor conduits, successfully simulating pain transmission behaviors similar to biological pain under acupuncture and dull pain stimulation. This type of artificial nociceptor enables the sensing and response to various types of noxious stimuli with higher accuracy and reliability. However, coupling sensors with artificial synapses in a decentralized deployment would inevitably increase the complexity of the integrated system and the manufacturing challenges for miniaturized devices.

Another promising integration strategy is to design single sensors with unique electrical response behaviors for pain perception. The regulation of nociception can be realized by adjusting the threshold response. Although the monolithic sensing structures could achieve effective integration, current integrated systems of single sensors unable to replicate the complex pain signal regulation process of natural biological skin. Recently, a neuro-inspired artificial electronic receptor prototype based on a bismuth selenide (Bi_2Se_3) memristor was developed for a highly efficient artificial thermal nociception system [7]. The combination of the blocking effect of the polymethyl methacrylate layer and the charge trapping/de-trapping in the Bi_2Se_3 layer enabled the realization of both threshold switching and resistive switching behaviors within a single device. The memristor not only mimics human nociceptor such as threshold, relaxation, and desensitization, but also reproduced high-fidelity responsiveness and pain reflexes based on environmental temperature sensing signals. Therefore, through reasonable material selection and structural design, efficient artificial nociceptors can be realized in highly integrated bionic systems.

Future research should focus on creating artificial nociceptors that can integrate and process multiple types of noxious stimuli, as well as explore the incorporation of biomimetic features that mimic the biological mechanisms of pain transmission (Fig. 1c). Currently, most artificial nociceptors are limited to sensing a single noxious stimulus, such as pressure or temperature. In contrast, multi-dimensional nociceptors are needed to detect multiple stimuli simultaneously, thereby providing a richer and more authentic pain perception for electronic devices. Additionally, investigations into the neural encoding of pain and the development of more sophisticated algorithms will be essential for enhancing the feedback behavior of these devices in response to various stimuli. With continued research and development, artificial nociceptors that emulate the human nervous system are expected to become integral components of artificial intelligence and automation technologies.

Shared outlooks. In pain management, abnormal pain is primarily alleviated by blocking pain signal transmission, while pain reconstruction seeks to restore natural pain perception by developing artificial nociceptors. As modern medical concepts evolve, pain management strategies have shifted from simple suppression to restoring normal pain perception. For example, in treating phantom limb pain, neuroleptic and opioid medications only alleviate some symptoms, but the pain often persists. Interestingly, reconstructing somatosensory feedback in severed limbs using closed-loop spinal cord stimulation significantly relieved persistent phantom limb pain. Sensitization-regulated artificial nociceptors have been developed by adjusting the channel thickness in electrolyte-gated transistors [8]. These artificial nociceptors, with adjustable sensitization, could help pain-sensitive individuals reduce pain sensations by normalizing hyperexcitable central neural activity. These findings suggest that future pain management may prioritize restoring normal pain perception over merely blocking pain signal transmission. Here, we focus on the shared trends in the development of electrical stimulation in both fields, with a view to providing a basis for future convergent communication (Fig. 2).

Flexible electronics for conformable bioelectronic interfaces. A significant hurdle in electrical stimulation for pain management and reconstruction is developing a reliable bioelectronic interface. Human tissues are mostly soft, wet, and curvilinear, while materials of electronics are rigid, dry, and planar. For example, the elastic modulus of brain tissue is about 1 to 4 kPa, while that of silicon, tungsten, and other metals or inorganic semiconductor materials typically exceeds 100 GPa. These mismatches limited the application of implanted medical electronics and even leads to serious complications, such as tissue damage, foreign body rejection, and device performance degradation. In addition, owing to the irregular motion of the tissue, electronics typically cannot absolutely realize synchronous movement with the dynamic tissues, which affect the quality of the transmitted electrophysiological signals. To get high quality and long term stable electrophysiological signals, it requires that the electrode is soft and conformable, so that the electrodes can move synchronously with the dynamic tissues.

The material composition and structural design of electrical stimulation electrodes play crucial roles in determining their mechanical performance (Fig. 2a). Intrinsically low-modulus materials have been developed and applied in conformable electronics, including organic material, liquid-phase materials, hydrogels, nanocomposites, etc. However, the conductivity of these low-modulus materials remains far lower than that of traditional conductive materials. To address the inherent rigidity of traditional conductive materials, structural designs have been proposed to develop conformal interfaces with biological tissues. These structural designs include mesh structures, interconnect designs, fractal designs, and kirigami designs. For example, the effective stiffness of a mesh structure is several orders of magnitude lower than that of a planar structure. By designing a honeycomb-like mesh architecture, conformal electronics based on indium-gallium-zinc oxide (an inherently brittle material) can improve the stretch of the electronics up to 10% without performance degradation [9].

Softening materials responsive to stimuli represent an important advancement in the development of conformable electrical stimulation devices. Typical soft electronic components conform to body curvature but face limitations in withstanding high contact forces and ease of operation. Softening bioelectronics address these challenges by maintaining initial rigidity for shape retention and then softening to adapt to the complex three-dimensional surfaces of organs, such as the brain and heart, or cylindrical tissues, such as nerves and the spinal cord. For instance, inspired by spider silk, a study designed water-responsive shape-adaptive polymer (WRAP) films [10]. WRAP films composed of poly(ethylene oxide) and poly(ethylene glycol)-α-cyclodextrin inclusion complex. These films are initially dry, flexible and stable under ambient conditions, contract by more than 50% of their original length within seconds (about 30% per second) after wetting and become soft (about 100 kPa) and stretchable (around 600%) hydrogel thin films thereafter. This film can be used to fabricate shape-adaptive electrode arrays conformally wrap around nerves through supercontraction, offering good mechanical match with nerve tissues.

Stable power and electrical signal generation are also important challenges for implantable electronics. The stability of the bioelectronic interface is susceptible to human physiological activities, which can cause motion artifacts that may disruptively affect the accuracy of electrical signal generation. In the design of conformal electronic interfaces, ensuring adequate adhesion performance is crucial for maintaining interface stability in complex dynamic environments. Soft bioelectronics can adapt and adhere to living tissues through physical interactions, capillary forces, surface microstructures and covalent chemical bonds. For example, an ultra-thin gelatin film can facilitate the formation of numerous hydrogen bonds through –OH and –COOH interactions in a slightly humid environment, thereby rapidly constructing a wet-adhesive interface without damaging tissue structure [11].

Despite the promising advancements in flexible electronic devices for bioelectronic interfaces, several limitations remain that must be addressed to fully realize their potential in pain management and perception. While flexible materials are essential for conformability and comfort, they often face challenges related to durability and long-term stability. Many soft materials may degrade over time, leading to reduced performance and requiring frequent replacements. Pain perception is a complex, multifactorial process influenced by various biological and psychological factors. Current bioelectronic interfaces may not fully capture the intricacies of pain signaling pathways, limiting their effectiveness in personalized pain management. While advances in miniaturization are promising, further work is needed to integrate multiple functionalities (e.g., stimulation, sensing, and data processing) into a single device without compromising performance. Achieving this integration while maintaining device flexibility and usability is a significant challenge. In conclusion, ongoing research and development in flexible electronic devices and bioelectronic interfaces are poised to transform pain management and perception, offering innovative solutions that prioritize both therapeutic effectiveness and patient quality of life.

Machine learning for pain perception. Machine learning (ML) has emerged as a transformative tool in optimizing electrical stimulation therapies for pain management. The intricate nature of pain perception, characterized by its subjective and multifaceted responses to electrical stimulation, presents significant challenges in designing effective neuromodulation protocols. Traditional methods often encounter computational limitations that hinder real-time adjustments and extensive exploration of stimulation parameters. In contrast, ML techniques can effectively address these challenges by providing efficient and accurate modeling of pain responses to electrical stimulation (Fig. 2b).

One of the primary applications of ML is the development of surrogate models for assessing pain by analyzing a multitude of physiological and behavioral data sources, such as heart rate, electromyogram, and facial expressions. By leveraging high-performance computing and parallel processing, these models facilitate rapid and timely prediction of pain occurrence, significantly enhancing computational efficiency while maintaining predictive accuracy. This capability is crucial for tailoring pain management strategies to individual patients, thereby improving the effectiveness of therapies such as spinal cord stimulation and peripheral nerve stimulation. Moreover, ML can facilitate real-time monitoring and dynamic adjustment of stimulation parameters based on individual pain responses. For example, wearable devices that track physiological signals related to pain can employ ML algorithms to analyze data in real time, enabling on-demand electrical stimulation that adapts to the patient's current pain levels [12]. This approach not only improves pain management by ensuring timely interventions but also enhances treatment effectiveness by customizing stimulation to each patient's unique pain profile.

In addition to optimizing parameters, ML plays a vital role in predicting treatment outcomes related to pain perception. Studies involving transcranial direct current stimulation have demonstrated that the benefits of stimulation can vary widely among individuals due to differences in neuroanatomical structures and

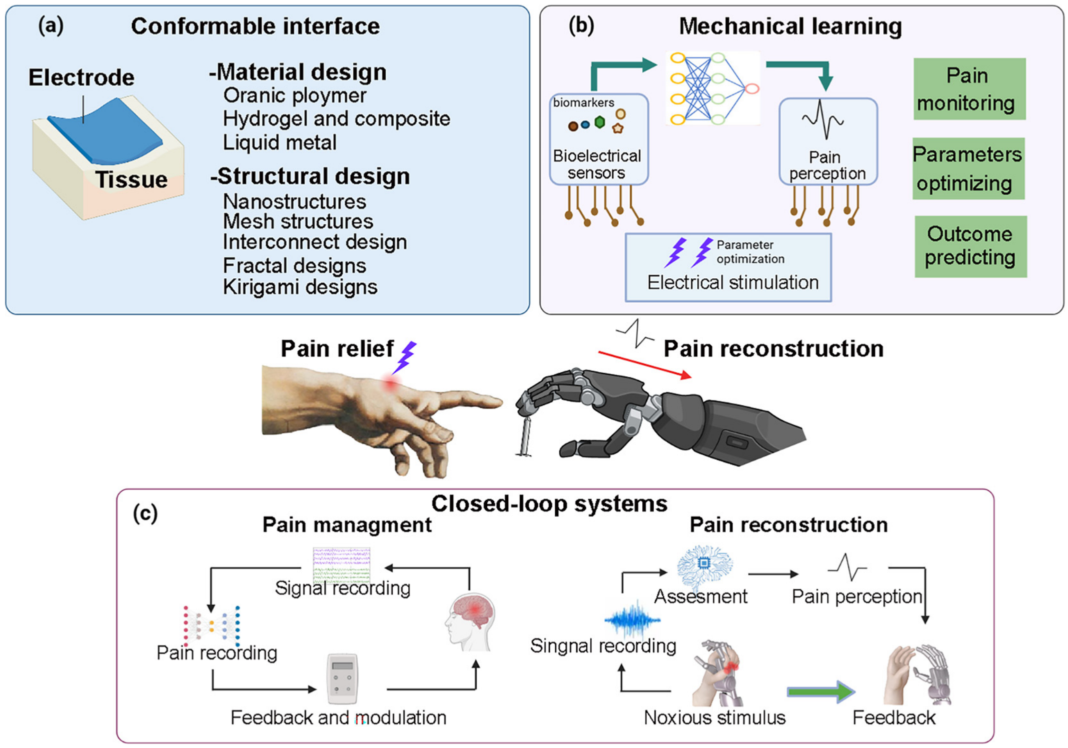

Fig. 2. The shared outlook of electrical stimulation in pain management and reconstruction. (a) Strategies for the development of conformal bioelectronic interfaces; (b) The utilization of machine learning in modulating pain through electrical stimulation; (c) Closed-loop systems in pain management and pain reconstruction. Created with Biorender.com.

pain pathways [13]. To address this variability, ML algorithms, such as support vector machines, can be trained to predict treatment responses based on computational models of current density affecting pain perception. These models have shown considerable success in optimizing stimulation parameters to maximize pain relief, achieving a high degree of coherence between predicted and actual responses in targeted pain pathways.

The subjectivity and individual variability in pain perception, influenced by a combination of psychological, cultural, and experiential factors, present significant challenges to the application of ML in pain reconstruction. Additionally, the variance in pain sensitivity and treatment response can be largely attributed to genetic factors. These factors complicate the development of universally effective pain assessment algorithms. As research continues to evolve, addressing these existing limitations through rigorous investigation and collaboration between ML, computational modeling, and clinical practice is essential for transforming the landscape of pain perception therapies, paving the way for innovative solutions that maximize therapeutic efficacy.

Closed-loop systems for feedback. Closed-loop systems represent a groundbreaking approach that allow the continuous automatic tracking and adjustment of interventions based on feedback, with a wide range of applications in pain management and pain reconstruction (Fig. 2c).

By automatically decoding nociceptive signals and applying therapeutic electrical stimulation, closed-loop systems offer an innovative model for pain management, allowing for timely interventions that can inhibit or mitigate pain before it is consciously experienced by the individual. Recently, a prototype closed-loop system for pain management was proposed that utilizes a brain-computer interface focused on the anterior cingulate cortex, a critical region involved in pain processing [14]. This system detects the onset of nociception and decodes these pain signals using a state-space model. The decoded pain activation signals trigger optogenetic stimulation in the prefrontal cortex, effectively modulating nociceptive sensations from a higher brain region. This regulation can prevent the downward transmission of pain signals, facilitating preemptive interventions that may reduce the perception of pain and enhance patient comfort. Moreover, the concept of closed-loop systems has been extended to various domains within pain management [15], including the "smart" bandages for chronic wound pain, the pain associated with movement impairment in stroke patients, and pain associated with cardiac dysfunction.

The reconstruction of pain feedback through closed-loop systems also offers great potential for the intelligent alarm systems, neuroprosthetics, and neurorobotics. A recent study proposed a closed-loop artificial pain regulation system to simulate the spinal cord's pain regulation function. Researchers fabricated Gd_xO_y and Al_xO_y charge-regulated field-effect transistors with a monolayer graphene channel, using them as inhibitory and excitatory synapses, respectively, under the same pulse signals to mimic the biological reflex arc through a connection with an actuator [16]. This setup provides a significant step forward to realizing the functions of the nervous system, giving promising potential for developing future intelligent systems.

Nevertheless, closed-loop control systems still face many challenges in the clinical practice. Clinical pain is a dynamic process, and closed-loop systems need to be able to adapt to changes in the brain over time. Current closed-loop control systems adjust the parameters of electrical stimulation through subjective feedback of pain, which is time-consuming and painful process. In this respect, integrating adaptive control algorithms into closed loop control system can offer a powerful new approach to pain regulation. Furthermore, the fidelity of brain-computer interface biomarker decoding may change over time for several reasons, including various technical or hardware issues, co-adaptive learning, and cognitive changes of the brain. Going forward, the development of closed-loop systems might pave the way for pain regulation by offering a more personalized, adaptable, and effective approach. However, much work will be needed before a machine can flexibly monitor and change pain patterns in the brain for therapeutic purposes.

Conclusion. Pain perception is a double-edged sword. While normal pain perception serves as the body's defense mechanism to avoid potential harm, long-term and persistent pain causes significant distress to individuals and society. The fundamental role of electrical signal in pain perception provides dual regulatory functions in pain regulation. Despite the current differences in focus, electrical stimulation faces shared goals and challenges in both pain management and reconstruction. This underscores the need to establish a bridge for communication and cooperation between the two fields. With the advent of new technologies, it is conceivable that electrical stimulation will be able to regulate pain more flexibly.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Nature Science Foundation of China (82471000 to KJ, 82325012 to LN) and National Key Research and Development Program (2023YFC2509100 to KJ). We thank State Key Laboratory of Oral and Maxillofacial Reconstruction and Regeneration for technical support.

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