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Decoding and canceling pain: paving the way for a brighter future in chronic pain management with AI-driven neurostimulation

Decodificando e cancelando a dor: o futuro da gestão da dor crônica com neuroestimulação guiada por IA

Decodificando y cancelando el dolor: el futuro del manejo del dolor crónico con neuroestimulación guiada por IA

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ABSTRACT

Objective: To present and summarize the concept of intelligent, closed-loop neuromodulation devices, which aim to identify the specific neural signatures of chronic pain and selectively cancel them. **Bibliographic review:** This narrative review explores a revolutionary approach at the intersection of neuroscience and artificial intelligence, treating chronic pain as a neural circuit pathology. It discusses how machine learning algorithms can decode complex neural data to isolate pain signals in real-time, enabling the identification of an objective biomarker. Based on this decoding, targeted neurostimulation can deliver precise interventions to disrupt these pathological signals, operating in a closed-loop system (sense-decode-actuate) that is more effective and safer than conventional open-loop therapies. This approach represents the transition from systemic treatments to an adaptive and personalized therapy. **Final considerations:** It can be considered that this AI-driven paradigm holds promise for a fundamental shift in pain management. By offering a personalized and specific therapy, it represents a potential solution for intractable pain conditions, redefining the treatment for a condition that affects millions and transforming a symptom into a treatable biological signal.

Keywords: Chronic pain, Artificial intelligence, Deep brain stimulation, Brain-computer interface, Brain stimulation techniques.

RESUMO

Objetivo: Apresentar e sumarizar o conceito de dispositivos de neuromodulação inteligentes e de malha fechada, que visam identificar as assinaturas neurais específicas da dor crônica e cancelá-las seletivamente. **Revisão bibliográfica:** Esta revisão narrativa explora uma abordagem revolucionária na interseção da neurociência e da inteligência artificial, tratando a dor crônica como uma patologia de circuito neural. Discute-se como os algoritmos de machine learning podem decodificar dados neurais complexos para isolar os sinais de dor em tempo real, permitindo a identificação de um biomarcador objetivo. A partir dessa decodificação, a neuroestimulação direcionada pode fornecer intervenções precisas para interromper estes sinais patológicos, operando em um sistema de malha fechada (sentir-decodificar-atuar) que é mais eficaz e seguro do que as terapias de malha aberta convencionais. Esta abordagem representa a transição de tratamentos sistêmicos para uma terapia adaptativa e personalizada. **Considerações finais:** Pode-se considerar que este paradigma impulsionado pela IA promete uma mudança fundamental no tratamento da dor. Ao oferecer uma terapia personalizada e específica, ele representa uma potencial solução para condições de dor intratável, redefinindo o tratamento de uma condição que afeta milhões de pessoas e transformando um sintoma em um sinal biológico tratável.

Palavras-chave: Dor crônica, Inteligência artificial, Estimulação cerebral profunda, Interface cérebro-computador, Técnicas de estimulação cerebral.

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RESUMEN

Objetivo: Presentar y resumir el concepto de dispositivos de neuromodulación inteligentes y de bucle cerrado, que buscan identificar las firmas neuronales específicas del dolor crónico y cancelarlas selectivamente. **Revisión bibliográfica:** Esta revisión narrativa explora un enfoque revolucionario en la intersección de la neurociencia y la inteligencia artificial, tratando el dolor crónico como una patología del circuito neural. Se discute cómo los algoritmos de machine learning pueden decodificar datos neuronales complejos para aislar las señales de dolor en tiempo real, permitiendo la identificación de un biomarcador objetivo. A partir de esta decodificación, la neuroestimulación dirigida puede administrar intervenciones precisas para interrumpir estas señales patológicas, operando en un sistema de bucle cerrado (sentir-decodificar-actuar) que es más eficaz y seguro que las terapias de bucle abierto convencionales. Este enfoque representa la transición de tratamientos sistémicos a una terapia adaptativa y personalizada. **Consideraciones finales:** Se puede considerar que este paradigma impulsado por la IA promete un cambio fundamental en el tratamiento del dolor. Al ofrecer una terapia personalizada y específica, representa una solución potencial para condiciones de dolor intratable, redefiniendo el tratamiento para una condición que afecta a millones de personas y transformando un síntoma en una señal biológica tratable.

Palabras clave: Dolor crónico, Inteligencia artificial, Estimulación cerebral profunda, Interfaz cerebro-computadora, Técnicas de estimulación cerebral.

INTRODUCTION

Chronic pain, defined as pain that persists or recurs for more than three months beyond the normal tissue healing period, represents one of the most debilitating and prevalent medical conditions globally (COHEN SP, et al., 2021). Far from being merely a prolonged symptom, chronic pain is now recognized as a complex disease in its own right, a silent epidemic that disrupts lives. Recent data from the World Health Organization and the Global Burden of Disease (GBD) confirm chronic pain as a leading cause of disability and reduced quality of life, with low back pain alone affecting an estimated 619 million people in 2020 (GBD 2021 LOW BACK PAIN COLLABORATORS, 2023).

In Brazil, the prevalence follows the global trend, affecting millions of individuals and overwhelming the healthcare system. The biopsychosocial implications are profound, trapping patients in a vicious cycle of pain, fear of movement, physical deconditioning, and psychological distress. This subjective nature often leads to a diagnostic odyssey, where the patient's suffering can be devalued or stigmatized due to the absence of objective clinical signs, drastically impacting functional capacity, mental health—with high rates of comorbidity with depression and anxiety—and overall well-being, culminating in social isolation (GBD 2016 DALYS AND HALE COLLABORATORS, 2017).

The socioeconomic impact is equally devastating. The costs associated with chronic pain are divided into direct costs, such as doctor visits, hospitalizations, surgical procedures, and medications, and indirect costs, including lost productivity, absenteeism, presenteeism (being at work but with reduced productivity), and early retirement, often exceeding the costs of diseases such as cancer and diabetes (STUBHAUG A, et al., 2024). This economic burden not only strains healthcare systems but also affects families' financial stability and national productivity. The clinical management of chronic pain poses a formidable challenge, as current therapeutic modalities often prove inadequate. The pharmacological approach, historically dominated by opioids, has demonstrated limited long-term efficacy for many non-cancer chronic pain conditions.

Phenomena such as the development of tolerance, which requires increasingly higher doses for the same analgesic effect, and opioid-induced hyperalgesia, a paradoxical state where pain treatment ultimately increases sensitivity to it, severely limit their usefulness and contribute to the opioid public health crisis (VOWLES KE, et al., 2015). Other pharmacological classes, such as nonsteroidal anti-inflammatory drugs or anticonvulsants, offer only partial relief for many and are often accompanied by their own profile of systemic side effects, further highlighting a profound therapeutic vacuum. Neuromodulation therapies, such as spinal cord stimulation (SCS), have emerged as one promising alternative for specific syndromes, such as post-laminectomy syndrome and complex regional pain syndrome (DEER TR, et al., 2017). These devices apply an electrical field to the spinal cord to modulate the transmission of pain signals.

However, traditional SCS systems operate in an "open loop" fashion, delivering continuous, preprogrammed stimulation regardless of the patient's actual pain state. This non-adaptive approach fails to consider the dynamic nature of the nervous system. Over time, neural circuits can adapt to the continuous, monolithic electrical input, a process that leads to therapeutic habituation and a progressive loss of efficacy. The brain essentially "learns" to ignore the therapeutic signal, rendering the device less effective.

Furthermore, these systems are susceptible to positional effects, where simple movements can alter the distance between the electrode and the neural target, leading to inconsistent therapy or sudden, uncomfortable spikes in stimulation. Crucially, the mechanism of action of these systems is based on masking the pain signal with another sensation (paresthesia), an approach analogous to drowning out a fire alarm with loud music instead of putting out the fire. The lack of real-time response to the patient's natural pain fluctuation is a fundamental limitation (LAM CM, et al., 2023).

In this context of urgent need for more effective and safe therapies, the convergence of computational neuroscience, biomedical engineering, and artificial intelligence (AI) is opening a new frontier. The emerging hypothesis is that chronic pain, at its core, can be understood as a pathological and anomalous pattern of neural activity that can be objectively identified and, theoretically, corrected. This insight drives the development of a new generation of neuromodulation devices: intelligent "closed-loop" systems that utilize AI to operate adaptively and responsively. The aim of this study is to present and summarize this revolutionary paradigm, exploring the potential of AI to decode the "neural signature" of pain and subsequently apply precise and targeted stimulation to "cancel" this pathological signal at its source, promising a truly personalized and potentially curative treatment.

BIBLIOGRAPHIC REVIEW

Chronic Pain as a Neural Circuitry Pathology

The understanding of chronic pain has evolved significantly, transitioning from a purely sensory model to one that considers it a complex disease of the central nervous system. The transition from acute to chronic pain involves processes of maladaptive neuroplasticity at multiple levels of the neuroaxis, from peripheral neurons to higher cortical areas (KUNER R and FLOR H, 2016).

Neuroplasticity, the brain's intrinsic ability to reorganize itself by forming new neural connections, is a fundamental mechanism for learning and memory. In the context of pain, this ability can become detrimental. Persistent nociceptive stimulation can induce a form of long-term potentiation (LTP) at the synapses of pain pathways, strengthening these connections in a manner analogous to memory consolidation. Over time, these circuits become hypersensitive and self-sustaining.

A key mechanism in this process is "central sensitization," a phenomenon in which neurons in the dorsal horn of the spinal cord and the brain become hyperexcitable. At the molecular level, this involves the activation of NMDA receptors, which are normally blocked at rest, leading to an influx of calcium that triggers intracellular signaling cascades. This results in increased neuronal excitability and a reduced activation threshold, causing the central nervous system to enter a state of high alert. This hyperexcitability results in an increased response to noxious stimuli (hyperalgesia) and the perception of pain from normally non-painful stimuli (allodynia) (WOOLF CJ, 2011). Essentially, the nervous system "learns" to be in a state of pain, and this state becomes independent of the initial peripheral injury, persisting as a pathological memory encoded in neural circuits.

This conceptualization of chronic pain as a "circuit disease" or "channelopathy" is critical, as it suggests that the ideal therapeutic target is not just the symptom, but the anomalous electrical activity that underlies it. Functional neuroimaging studies in humans, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), have revealed that the experience of chronic pain is associated with altered activity patterns in a network of brain regions often referred to as the "pain matrix" (APKHARIAN AV, et al., 2010). These regions include the somatosensory cortex, the anterior cingulate cortex, the thalamus, and the insula.

Of particular importance, the insular cortex acts as an integrative hub, connecting the sensory-discriminative dimension of pain (its location and intensity) with its affective-motivational dimension (how unpleasant and emotionally distressing it is). The insula is therefore crucial to the subjective experience of pain-associated distress. Importantly, chronic pain is also associated with changes in functional connectivity between these regions and others, such as the prefrontal cortex, which is involved in the emotional and cognitive aspects of pain (HASHIMI JA, et al., 2013). This aberrant and sustained neural activity constitutes the biological basis that, in theory, can be measured and modulated.

Decoding the Neural Signature of Pain with Artificial Intelligence

Identifying an objective biomarker for pain is one of the most sought-after goals in medicine, as it would transform pain assessment from a purely subjective measure to a biological quantification. AI, and particularly machine learning algorithms, provide the computational tools necessary to decipher the complex, multidimensional patterns of neural activity and identify a "neural signature" of pain (SHOU G, et al., 2020). The process of developing a personalized pain decoder can be divided into several crucial steps. First, the data acquisition phase, where neural data are collected simultaneously with the patient's subjective reports of pain, typically on a numerical scale from 0 to 10.

This step is crucial to creating a dataset that correlates objective brain activity with subjective experience. Next, feature extraction occurs. The raw neural signal is extremely complex and noisy. Rather than analyzing the entire waveform, AI algorithms are trained to extract informative "features" from the signal. These features may include power in different frequency bands (such as alpha, beta, and gamma), coherence or functional connectivity between different brain regions, or the shape of specific oscillations. The hypothesis is that the signature of pain lies not in the raw signal, but in a specific combination of these features. The third step is model training. Using the labeled dataset, a machine learning model is trained to learn the mapping between neural features and reported pain levels.

Simpler algorithms, such as support vector machines (SVMs), are effective for classification tasks, such as distinguishing a "high pain" state from a "low pain" state. For more refined analysis, such as predicting exact pain intensity on a continuous scale, deep neural networks (DNNs) are more suitable, as they can model the nonlinear and complex relationships between multiple neural features and pain perception (SHIRVALKAR P, et al., 2023). Once trained and validated on unseen data, the system can ideally predict the presence and intensity of pain based solely on neural data, objectively (WAGER TD, et al., 2013). This real-time decoding capability is the cornerstone for building a closed-loop neuromodulation system.

Clinical Application of AI in Neural Biomarker Detection

The search for a reliable pain biomarker has led to the comparison of several neuroimaging modalities, each with its own advantages and disadvantages for real-time application. EEG measures electrical activity from the scalp, offering excellent temporal resolution. AI algorithms can be trained to identify changes in specific frequency bands, such as an increase in gamma-band activity or a suppression of the alpha band, which have been correlated with pain perception (ZEHBAUSER PT, et al., 2023). However, its spatial resolution is poor due to the volume conduction effect of the skull, and the signal is highly susceptible to movement artifacts and muscle activity, making it challenging to use in uncontrolled environments and for the precise localization of deep therapeutic targets. In contrast, fMRI measures changes in cerebral blood flow.

Its greatest advantage is its excellent spatial resolution, enabling the development of "neurological pain signatures" (NPS), which are patterns of activity across multiple brain regions that predict pain with high sensitivity. However, its low temporal resolution—resulting from measuring the slow hemodynamic response that is an indirect proxy for neural activity—its high cost, and the non-portable nature of the equipment make it unsuitable for real-time neuromodulation, making it more useful for research and identification of therapeutic targets.

For application in closed-loop systems, local field potentials (LFPs), recorded by implanted electrodes, stand out as the most promising modality. They capture the aggregate electrical activity of a population of

neurons, reflecting circuit oscillations that are crucial for pain coding. Because they are invasive, they offer a signal with a high signal-to-noise ratio and the spatial and temporal precision necessary to identify the pain signature in a specific circuit and subsequently apply stimulation precisely where and when needed. AI is crucial for analyzing these complex LFP signals. The brain is never electrically silent, so the challenge is not simply detecting a signal, but discriminating it.

AI must perform sophisticated real-time signal processing to isolate the specific biomarker of pain from the immense "cacophony" of other simultaneous neural processes, such as thoughts, emotions, or motor planning. It's not just about finding a needle in a haystack, but about identifying the signature of a specific needle when it's mixed in with countless other similar-looking needles—a task that would be impossible for a human observer. The ability to objectify pain in this manner could revolutionize not only treatment but also its diagnosis, the monitoring of therapeutic efficacy in clinical trials, and even the validation of pain complaints in legal and insurance settings, combating the stigma often associated with this condition.

Closed-Loop Neuromodulation: The Adaptive Therapeutic Paradigm

The concept of closed-loop neuromodulation represents the natural evolution of open-loop systems, where AI plays its most crucial role. Unlike continuous stimulation, a closed-loop system operates on an intelligent and adaptive cycle: sense, decode, and actuate (KNOTKOVA H, et al., 2021). First, implanted electrodes act as sensors, continuously monitoring the neural activity of the target circuit with high fidelity. Second, an integrated processor, running the pre-trained AI algorithm, acts as a decoder. The role of the decoder is not a simple binary switch; it must make subtle decisions in milliseconds, analyzing the neural data stream to determine not only if and when to stimulate, but also how—adjusting parameters such as frequency, amplitude, and waveform to optimize the therapeutic response.

Third, the same electrodes (or a different set) act as actuators, delivering a precise and targeted electrical pulse. This stimulation is highly sophisticated; It can be designed to be either "disruptive," such as a high-frequency burst to desynchronize pathological hypersynchrony, or "restorative," attempting to resynchronize the circuit to a healthier, non-nociceptive pattern of activity. This paradigm is not theoretical; it is clinically validated in other circuit-based neurological diseases.

For example, the RNS® System for epilepsy detects the onset of a seizure and applies stimulation to suppress it before it becomes widespread (HECK CN, et al., 2014). Similarly, adaptive DBS for Parkinson's disease adjusts stimulation parameters in real time based on neural biomarkers of motor symptoms, such as tremor (LITTLE S, et al., 2013). Success in these fields provides a robust proof of concept because, like epilepsy and Parkinson's, chronic pain is increasingly understood as a pathology of aberrant neural oscillations.

Applying this principle to chronic pain is the next logical step. Stimulation would be administered only when the pain signature is detected, which would offer several advantages: it would increase efficacy by targeting the pathological activity at its source, before the pain state fully consolidates; it would significantly reduce the device's battery consumption, resulting in fewer invasive replacement surgeries for the patient; and, crucially, it would minimize side effects such as paresthesia by avoiding continuous and unnecessary stimulation, potentially operating below the threshold of perception (RAZA A, et al., 2023). A final, and perhaps most profound, advantage lies in its ability to induce long-term therapeutic neuroplasticity. By repeatedly interrupting the pathological circuit, the system can gradually "teach" the brain to unlearn the chronic pain state, potentially leading to sustained relief even when the device is inactive.

Technical, Ethical Challenges, and the Future of Therapy

Despite their immense potential, the realization of AI-based pain-canceling devices faces significant challenges. Technically, the robustness and long-term biocompatibility of implanted electrodes are ongoing concerns. Scar tissue formation around the electrodes can degrade signal quality over time, requiring algorithm recalibration. The precise "neural code" for pain is incredibly complex, can vary between individuals, and evolves over time due to neuroplasticity, requiring AI algorithms to be able to continually readapt (PLONER M,

et al., 2017). The accuracy of these algorithms is critical; false positives could lead to unnecessary stimulation, while false negatives would result in failure to relieve pain.

Real-time calibration to adjust to the neuroplasticity of the patient's brain is a formidable engineering hurdle, especially considering the trade-off between battery life and the computational power required to run deep learning algorithms on a low-power implantable device. Beyond the technical challenges, profound ethical questions arise. Neural privacy is a paramount concern. Neural data is perhaps the most intimate form of personal information, revealing not only pain states but potentially emotional and cognitive states. Securing this data against unauthorized access, whether by hackers or for commercial purposes, is of paramount importance (DREW LR, 2019).

The possibility of "mind reading," even if rudimentary, demands a new category of rights: neurorights. The ability to directly modulate a subjective experience like pain raises questions about patient autonomy and personal identity. If an algorithm is making real-time decisions to suppress a sensation, to what extent does the patient remain in control? What does it mean to "turn off" a sensation that, while unpleasant, may have a protective function or be part of an individual's lived experience? Complete pain suppression could lead to risky behaviors or mask new injuries.

This forces us to question whether the goal should be the elimination of pain or its modulation to a manageable level, preserving the patient's autonomy to interpret their own body's signals. Informed consent for such procedures must be exceptionally rigorous. How can a patient fully consent to a technology whose long-term effects on brain structure and personality are unknown? This may require a model of "dynamic consent," where dialogue and permission are ongoing processes, not a one-time event.

Finally, practical feasibility and equity of access are critical barriers. The path to regulatory approval by agencies like ANVISA or the FDA will be long and complex, as current frameworks are built to evaluate static devices with predictable outputs, not dynamic systems whose therapeutic algorithms evolve. Regulators will need to develop innovative methods to validate the safety of these "living" algorithms and ensure that their decisions remain within safe and ethical boundaries. Furthermore, the high cost and the need for specialized hospital infrastructure may create a "neuro-chasm" where only the wealthy can access these therapies, deepening health inequalities.

This is particularly concerning given that the burden of chronic pain often falls most heavily on populations with fewer resources, meaning the technology could inadvertently widen the very health disparities it aims to address. Public debate and careful regulation are crucial to ensure that this technology is developed and implemented ethically and responsibly (HAAG L, et al., 2025). Studies like Shirvalkar's, which demonstrated prediction of chronic pain status using intracranial biomarkers, provide essential proof of concept but also underscore the urgency of addressing these ethical issues before clinical dissemination (SHIRVALKAR P, et al., 2023).

However, overcoming these challenges unlocks a future where the prospects for this technology transcend pain management. The ability to selectively modulate neural circuits could have a revolutionary impact on other areas. In neurological rehabilitation, targeted stimulation could strengthen motor pathways to accelerate recovery after a stroke. In psychiatry, modulating circuits such as the subgenual cingulate cortex could offer new hope for treating conditions like refractory depression and obsessive-compulsive disorder. Specifically for neuropathic pain, a notoriously difficult condition to treat, this circuit-targeted approach holds particular promise. Moreover, the technological horizon is expanding beyond implanted electrodes to include non-invasive methods, such as transcranial focused ultrasound, which shows potential for modulating deep neural circuits without the need for surgery, albeit with different considerations for spatial precision (LEGON W, et al., 2018).

The impact extends beyond treatment; the ability to objectify pain could revolutionize its diagnosis, the monitoring of therapeutic efficacy in clinical trials, and even the validation of pain complaints in legal and insurance settings, combating the stigma often associated with this condition. To ensure this future is equitable and safe, it is imperative to develop a collaborative and proactive framework, involving neuroscientists,

engineers, ethicists, patients, and policymakers, to guide the development and responsible implementation of this powerful technology.

FINAL CONSIDERATIONS

Artificial intelligence is poised to catalyze a paradigm shift in the treatment of chronic pain, transforming it from a subjective condition into an objectively measurable and treatable neural circuit pathology. This review has argued that the development of AI-driven, closed-loop neuromodulation systems—which transition from masking a symptom to decoding and correcting a biological signal—represents the most promising frontier. By offering effective pain relief with minimal side effects, this approach can restore quality of life, dignity, and even revolutionize diagnosis and validation in clinical and legal settings. While the future prospects of this technology extend to other areas like neurological rehabilitation and psychiatry, the path to clinical implementation requires overcoming significant technical and ethical challenges. The trajectory points unequivocally to a future where pain is treated as a signal to be decoded at its source, and ensuring this future is equitable requires a collaborative framework between scientists, engineers, ethicists, and patients to guide its responsible development.

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