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NARRATIVE REVIEW

Transcranial Direct Current Stimulation in Chronic Pain: Historical Perspective, Neurophysiological Mechanisms and Clinical Evidences.

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ABSTRACT

Chronic pain is a highly prevalent and disabling condition and is currently recognized as a disease sustained by maladaptive neuroplasticity and dysfunction of central pain-modulating networks. Despite major advances in pharmacological therapies, a significant proportion of patients experience insufficient analgesia, functional impairment, and reduced quality of life, underscoring the need for mechanism-based, non-pharmacological treatment strategies.

This review aims to summarize the historical background, neurophysiological foundations, clinical evidence, safety profile, and current limitations of transcranial direct current stimulation in the treatment of chronic pain, with particular emphasis on fibromyalgia and headache disorders.

A narrative review of experimental and clinical literature was conducted, including randomized controlled trials, systematic reviews, meta-analyses, and international guidelines. The analysis focused on neurophysiological mechanisms of transcranial direct current stimulation and its clinical application across major chronic pain syndromes.

Transcranial direct current stimulation exerts polarity-dependent modulation of neuronal excitability by inducing subthreshold shifts in the transmembrane potential, thereby altering neuronal firing probability and promoting N-methyl-D-aspartate receptor dependent synaptic plasticity. Importantly, its effects extend beyond local cortical modulation, influencing distributed pain-related networks involving the primary motor cortex, thalamus, insula, and cingulate cortex. Clinically, the most consistent evidence supports the use of anodal transcranial direct current stimulation over the primary motor cortex in fibromyalgia and migraine, demonstrating moderate reductions in pain intensity, attack frequency, and disease burden. Evidence in neuropathic pain and chronic low back pain is more heterogeneous but suggests potential benefit when transcranial direct current stimulation is applied in repeated sessions and integrated into multimodal treatment approaches. Across studies, transcranial direct current stimulation shows a favorable safety profile, with predominantly mild and transient adverse effects.

Transcranial direct current stimulation represents a safe, low-cost, and biologically grounded adjuvant therapy for chronic pain, particularly in conditions characterized by central sensitization and network-level dysfunction. While not a standalone intervention, its integration into multidisciplinary pain management strategies may enhance clinical outcomes and reduce reliance on long-term pharmacological treatments. Further large-scale, methodologically standardized trials are needed to refine stimulation protocols and identify patient subgroups most likely to benefit.

Keywords: tDCS, chronic pain, neuromodulation, fibromyalgia, migraine

Introduction

Fibromyalgia, neck pain, and headache are among the main causes of chronic pain, in addition to neuropathic pain and chronic cancer pain. Despite the significant evolution of pharmacological treatments in recent decades, the management of chronic pain remains one of the greatest challenges of contemporary medicine. Accumulated evidence demonstrates that, although various analgesic drugs are available, including anti-inflammatories, opioids, antidepressants, and anticonvulsants, a substantial proportion of patients continue to experience insufficient pain relief, significant functional limitations, and relevant impairment of quality of life. Pain is an unpleasant sensory and emotional experience, causing suffering that reduces quality of life. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage"[1]. Pain can be acute or chronic, with chronic pain persisting for more than 3 months beyond the expected healing time of the injury. It is estimated that 30% of the population is affected by some type of chronic pain, being the leading cause of years lived with disability worldwide. Low back pain is the leading single cause of global disability[2].

Furthermore, the prolonged use of analgesic drugs is often limited by adverse effects, development of tolerance, and risk of dependence, especially in the case of opioids, which restricts their long-term clinical benefit and poses ethical and safety dilemmas in the treatment of persistent pain. As a consequence, many patients remain in continuous suffering despite following pharmacological regimens considered technically adequate. This limited therapeutic performance largely reflects the heterogeneous and complex nature of chronic pain, which can no longer be understood merely as a symptom, but rather as a pathological condition in its own right, sustained by persistent alterations in the nociceptive and central modulator systems[3].In many patients, central sensitization mechanisms and nociplasticity perpetuate the painful experience even after the resolution of the initial peripheral insult, reducing the effectiveness of drugs traditionally targeting peripheral targets[4].

In light of contemporary knowledge in the neuroscience of pain, it has become evident that chronic pain is not only a consequence of persistent peripheral stimuli, but largely results from maladaptive neuroplasticity processes, in which central neural circuits autonomously sustain and amplify the painful experience. These dysfunctional circuits, characterized by central sensitization, loss of descending inhibition, and pathological reverberation of cortical and subcortical networks, maintain pain perception even in the absence of active tissue damage. From this conceptual framework, non-invasive neuromodulation emerges as a promising therapeutic strategy, with particular emphasis on Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). These methods act by modulating cortical excitability and synaptic plasticity, inducing lasting changes in the neural circuits involved in pain, with the potential to restore inhibitory mechanisms and modulate central hyperexcitability[5].

In addition to their neurobiological rationale, both TMS and tDCS have a favorable safety profile, with adverse events generally mild and transient when applied according to standardized protocols. Systematic reviews and international guidelines recognize these techniques as safe and potentially effective options in the treatment of various chronic pain syndromes, reinforcing their growing role in contemporary clinical practice[6]. In this article, we will focus on tDCS, a therapeutic procedure with an excellent safety profile, low cost, and good potential for efficacy.

Historical perspectives of tDCS

Research involving tDCS in the treatment of neuropsychiatric pathologies has grown exponentially in the last two decades, driven by advances in knowledge about neuroplasticity, maladaptive brain circuits, and modulation of cortical excitability[7]. However, despite its contemporary technological nature, the use of electricity as a therapeutic tool in the treatment of brain diseases has deep historical roots, dating back to Antiquity[8] .

One of the earliest documented records of the therapeutic use of electricity dates back to the 1st century AD, with Scribonius Largus, personal

physician to the Roman emperor Claudius. In his work Compositiones Medicamentorum (46 AD), Scribonius described the use of electric fish of the genus Torpedo applied directly to the scalp or other areas of the body for the treatment of severe headaches, gout, and chronic pain, empirically recognizing the analgesic effect of electrical discharges. This account is considered the first systematized record of electrotherapy in the history of medicine.

During the following centuries, interest in biological electricity remained intermittent until it was decisively resumed in the 18th century, with the experiments of Luigi Galvani, who demonstrated the existence of so-called "animal electricity" by observing muscle contractions induced by electrical stimuli in nerve tissues. Galvani's discoveries established the foundations of modern electrophysiology and consolidated the notion that electrical phenomena are intrinsic to the functioning of the nervous system[9].

In the 19th century, researchers like Giovanni Aldini, Galvani's nephew, advanced the application of electrical stimulation directly to the human brain, conducting pioneering transcranial stimulation experiments for therapeutic purposes, including attempts to treat "severe melancholia" and other neuropsychiatric disorders. Although these procedures lacked standardization and mechanistic understanding, they anticipated central concepts of modern neuromodulation.

Throughout the early 20th century, various forms of brain electrotherapy were used empirically, culminating in the development of electroconvulsive therapy (ECT), which remains an effective intervention for treatment-resistant depression to this day. However, only with the advent of modern neuroscience, bioengineering, and functional neuroimaging techniques has it been possible to understand precisely how weak electrical fields modulate synaptic activity and neuronal plasticity.

In this context, tDCS emerges as the scientific and safe evolution of a millennial therapeutic concept, allowing the controlled modulation of cortical excitability through low-intensity currents, with an excellent safety profile and growing clinical evidence in various neurological and psychiatric pathologies[9]. Thus, contemporary non-invasive neuromodulation represents not a historical rupture, but the technological and conceptual maturation of medical practices initiated almost two millennia ago.

Neurophysiological Fundamentals

Transcranial direct current stimulation is a non-invasive neuromodulation technique based on the application of low-intensity electrical currents (typically between 1 and 2 mA) through the scalp, capable of crossing the skull and generating weak, yet biologically relevant, electrical fields in the underlying brain tissue. Unlike techniques that directly induce action potentials (TMS), tDCS acts more subtly, modulating neuronal activity by altering the functional state of cortical and subcortical networks.

The main immediate neurophysiological mechanism of tDCS lies in the modification of the neuronal transmembrane potential. The application of a continuous electric field causes a partial change in the neuronal membrane. Anodic stimulation tends to facilitate depolarization, bringing the resting potential closer to the firing threshold and, consequently, facilitating the generation of action potentials in response to physiological synaptic stimuli. Cathodic stimulation, in turn, promotes relative hyperpolarization, moving the membrane potential away from the firing threshold and reducing local neuronal excitability[10].

In addition to the immediate effects on membrane potential, tDCS induces lasting changes in cortical excitability, which persist after the end of stimulation. Experimental evidence demonstrates that these late effects are mediated by N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity mechanisms, sharing molecular pathways similar to long-term potentiation and depression (LTP/LTD)[11]. Pharmacological studies have shown that NMDA receptor antagonists block the prolonged effects of tDCS, while glutamatergic modulators can potentiate them, reinforcing the central role of synaptic plasticity in consolidating the therapeutic effects of the technique[12].

Regarding the use of this method in chronic pain, research has been reinforcing the choice of the primary motor cortex (M1) as the preferred target for anodal stimulation by tDCS, based on a consistent body of neurophysiological, neuroanatomical, and

clinical evidence. Although M1 (C3 in the 10-20 system used in EEG) is classically associated with voluntary motor control, it is now widely recognized that this region plays a central role in the descending modulation of pain, integrating cortico-subcortical networks involved in the sensory, emotional, and cognitive processing of the painful experience. From a general point of view, the effectiveness of anodal stimulation in M1 is not only due to a local excitability-increasing effect, but also to its ability to reorganize distributed circuits involving the thalamus, insula, cingulate gyrus, and other cortical and subcortical areas. Small changes in the excitability state of M1 can reverberate throughout these networks, promoting adaptive plasticity and restoring inhibitory mechanisms compromised in chronic pain[13]. This understanding makes the use of M1 neurophysiologically rational, predictable, and aligned with the modern model of pain as a brain circuitry disease. Thus, anodal tDCS on the primary motor cortex represents a well-founded strategy to interfere at multiple levels of pain processing.

Clinical evidence of tDCS in chronic pain

This non-invasive neuromodulation method has been investigated in multiple chronic pain syndromes, with a consistent mechanistic rationale (modulation of M1/dorsolateral pré-frontal cortex and thalamus-insula-cingulate networks) and a favorable safety profile. In general, studies show modest to moderate benefits, with significant heterogeneity between protocols (target, polarity, dose, number of sessions) and between pain phenotypes, reinforcing the need for appropriate patient selection and mechanism-driven protocols[14].

Among chronic pain conditions, fibromyalgia is one of those with the most consistent evidence for non-invasive neuromodulation, especially with anodal M1 stimulation. In the "proof-of-principle," randomized, sham-controlled study, tDCS on M1 showed improvement in pain and clinical outcomes, stimulating a line of research that has expanded with different designs and protocols[15]. In addition, optimized protocols, including more focal assemblies (e.g., high-definition tDCS), have also been evaluated in randomized clinical trials, reinforcing the therapeutic plausibility in pain and functional impact[16]. There is also evidence of the potentiation of tDCS action in relieving fibromyalgia pain when associated with physical activity[17].

For primary headaches, the body of RCTs and meta-analyses suggests that tDCS can reduce migraine days (prophylaxis), with effects varying according to the target (M1, visual cortex, dorsolateral pré-frontal cortex) and polarity. In chronic resistant migraine, there is relevant clinical evidence of a prolonged prophylactic effect with anodal tDCS applied to the left M1, with maintenance of the benefit for weeks after the stimulation period in a randomized pilot trial[18].

In neuropathic pain, especially in conditions such as painful diabetic polyneuropathy, there are randomized controlled trials suggesting benefit with tDCS on M1. A sham-controlled RCT demonstrated pain relief after daily tDCS sessions on M1, with maintenance for weeks[19]. Evidence-based guidelines for tDCS recognize possible efficacy (depending on the indication and protocol) for some neuropathic pain conditions, with M1 as a frequent and rational target[20].

In chronic low back pain, systematic reviews indicate heterogeneous results, with a tendency towards a better response when tDCS is combined with active intervention (e.g., exercise, motor training) and applied at an appropriate dose. One systematic review evaluated the effectiveness of tDCS in nonspecific chronic low back pain and discusses methodological limitations and effect variation[21]. Pilot trials combining tDCS and exercise have also been published, supporting the hypothesis of potentiation by a multimodal approach.

Safety profile and limitations in tDCS

Transcranial direct current stimulation (tDCS) is widely recognized as a non-invasive, well-tolerated neuromodulation technique with a favorable safety profile, especially when compared to chronic pharmacological interventions or invasive methods. This profile has decisively contributed to the rapid expansion of clinical and translational studies in the last two decades[22].

Despite its good safety profile, tDCS has important limitations that must be recognized for rational

clinical application. The main one is the interindividual variability in response, widely documented in the literature. Anatomical, physiological, and behavioral factors influence the effects of stimulation. Another relevant limitation concerns the heterogeneity of clinical protocols. Differences in cortical target, polarity, intensity, duration, and number of sessions hinder direct comparison between studies and contribute to inconsistent results in meta-analyses, especially in complex conditions such as chronic pain. Furthermore, the clinical effects of tDCS tend to be modest in magnitude, rarely sufficient as a standalone intervention. Current literature suggests that its greatest therapeutic value lies in combination with other therapeutic strategies. Controlled clinical trials, systematic reviews, and international guidelines demonstrate that adverse events associated with tDCS are generally mild, transient, and self-limiting. The most frequently reported effects include itching, tingling sensation, mild burning at the electrode site, slight headache, and transient fatigue after the session[22].

Among the main controversies surrounding tDCS is the difficulty in reproducing clinical effects, especially in studies with small samples. Recent meta-analyses have raised questions about the risk of publication bias and the overestimation of effects in initial studies, requiring greater methodological rigor and large-scale multicenter trials[23].

Conclusion

tDCS is a promising therapy for the treatment of chronic pain, presenting itself as a low-cost treatment with an excellent safety profile and a real possibility of good efficacy. In clinical practice, we observe good results on a daily basis, especially in chronic migraine and, mainly, in fibromyalgia.

This method can consolidate itself as an important adjuvant therapy in chronic pain, reducing the use of medications and significantly alleviating the suffering of patients. However, we need more robust data, which will come with the standardization of the application of the method (stimulation site, polarity, intensity, current density, stimulation time, interval between stimuli, number of sessions and treatment period). Publications have increased exponentially and with a greater number of patients studied. It is possible to believe that soon we will have many positive answers regarding tDCS in the treatment of chronic pain, placing it as another weapon in the therapeutic arsenal for the relief of long-term pain.

Conflict of Interest Statement

There is no conflict of interest for this article.

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