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The pros and cons of tDCS as a therapeutic tool in the rehabilitation of chronic pain

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INTRODUCTION

Chronic pain is defined as a pain that lasts longer than three to six months, with symptoms that remain beyond usual tissue healing duration of 6 to 12 weeks after an acutely painful event or occurs along with a chronic health condition. Chronic pain presents a tremendous burden on society, the afflicted individuals' lives, and their family members, with prevalence affecting approximately 20.5% of the United States population (50.2 million) and 8.0% affected by high-impact chronic pain (19.6 million) that frequently limits activities of daily living, mobility and work functioning (Yong et al., 2022, Zelaya et al., 2020). Chronic pain is one of the most common reasons adults seek medical care, and has been linked to dependence on opioids, anxiety, depression, and poor perceived health or reduced quality of life (Dahlhamer et al., 2018).

Chronic pain can arise from a combination of biomechanical, neurologic, psychological, nutritional, hormonal and social components and can lead to a degree of central sensitization that refers to the amplification of pain by supraspinal central nervous system mechanisms including increased responsiveness or recruitment of nociceptive neurons to normal or subthreshold afferent input, either with ongoing nociceptive input or in the absence of a peripheral driver (Harte et al., 2018, Colloca et al., 2017).

Overview of tDCS research development

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique where low-amplitude sub-threshold direct currents are applied across the scalp to produce localized changes of cerebral excitability and modulate neuronal excitability. The first pioneering use of tDCS on the human scalp was published in 2000 by Dr. Michael Nitsche and Dr. Walter Paulus's clinical research group at the University of Gottingen (Nitsche and Paulus, 2000). The first clinical trials using tDCS for management of chronic pain including fibromyalgia was published in 2006 by Dr. Felipe Fregni's clinical research group at Harvard University (Fregni et al., 2006). Since then, multiple groups have joined in the pioneering work and the technique has continued to evolve, with clinical application findings that tDCS can facilitate post-stroke recovery of residual motor and speech deficits and provide relief from various forms of chronic pain (Lefaucheur, 2017) including fibromyalgia, osteoarthritis, low back, phantom limb pain and neuropathic pain from spinal cord injury, especially when applied with other therapies, such as visual illusion (Soler, 2010).

tDCS has the potential to become a clinically-relevant therapeutic tool either being used asynchronously, i.e., priming the central nervous system to other therapies, or synchronously combined with standard of care rehabilitation of chronic pain including physical

therapy, pharmaceutical and interventional management. Current medicine-based guidelines support the use of anodal tDCS over the motor cortex in conditions including neuropathic pain, fibromyalgia and migraine with a level B of recommendation (Fregni et al, 2021). tDCS induces cortical electric fields and neuroplasticity-targeted excitability changes in the human cortex by mechanisms of synaptic modification and long-term potentiation or depression, resulting in persistent changes along synapses based on recent patterns of activity (Hess 1996). This is performed by applying subthreshold excitatory anodal current stimuli typically to motor cortical regions contralateral to the area of most pain. It is generally understood that surface-positive anodal current promotes facilitatory effects whereas a surface-negative cathodal current promotes inhibitory effects over targeted areas or circuits.

Pros of tDCS as a therapeutic tool in the rehabilitation of chronic pain

Facilitates understanding of central mechanisms underlying chronic pain and represents an effective tool to induce neuronal plasticity to promote descending cortical pain inhibition by enhancing excitatory motor facilitation

tDCS contributes to the understanding of underlying mechanisms and rehabilitation of chronic pain sensitization, with potential to elicit therapeutic benefit by facilitating reversal of maladaptive plasticity by augmenting excitatory motor facilitation and thereby upregulating descending anti-nociceptive intracortical inhibitory mechanisms, without dampening function of the sensory cortex. These cortical excitability changes of enhancing neuronal firing and increasing size of evoked potentials by an applied polarizing direct current has been systematically characterized over decades and demonstrated in animal, in-vitro and human models with resulting long-lasting plasticity effects (Bindman et al, 1964). Supporting this notion, studies have found enhancement of the endogenous pain modulation system, measured by conditioned pain modulation after anodal motor cortex tDCS stimulation (Giannoni-Luza et al, 2020). Whereas alternative therapies such as physical therapy approaches chronic pain rehabilitation primarily via bottom-up peripheral mechanisms that contribute to neural changes, tDCS provides an additive approach with electrical stimulation applied via central mechanisms to improve intracortical and top-down pain inhibition.

Inexpensive and ease of application

tDCS has distinct advantages of being inexpensive and easy to administer. tDCS is a non-invasive technique, mainly consisting of electrodes placed on the scalp providing a low electric current (Thair et al. 2017, Pacheco-Barrios et al. 2020). The main difficulties are related to defining the optimal electrode placement and stimulation parameters to specific pain conditions, including anodal and cathodal electrodes location, intensity, duration, number of sessions and the use or not of a concomitant therapy, but after deciding these parameters it's feasible to replicate this throughout the follow-up. Also, tDCS equipment including electrodes are relatively inexpensive and the same tDCS device can be used for many different patients, making it an accessible technique. Previous studies have found a cost-effective benefit of using tDCS in patients with neuropathic pain after spinal cord injury compared to standard pharmacological care (Xi et al, 2021), however, more studies are needed . When a different approach is necessary - even for non-painful conditions -, it is possible to use HD-tDCS, which is associated with a more focused and longer-lasting neuromodulatory effect (Parlikar et al. 2021).

Safe and non-invasive for routine application

tDCS has a benign profile of adverse events and invasiveness: the cumulative charge of a commonly used tDCS treatment, calculated as the product of the current intensity x the duration x the number of sessions, is not associated with irreversible injuries and the trials showed little to no collateral damages (Bikson et al. 2016). It is possible to have side effects, but they are mild and short-lived, despite many studies not accessing this information. There are no reports of serious adverse effects (Fregni et al. 2016). For this, tDCS can also be used on healthy subjects for research purposes.

Can be used in a wide range of environments including a home-based treatment possibility

Many studies suggest long protocols for tDCS interventions (Fregni et al. 2006), since an increase in the number of sessions leads to longer-lasting effects of the therapy. This makes it harder for chronic patients in

the clinical setting, and the need for regular medical appointments is an eventual explanation for observed loss of follow-up of up to 75% in some studies (Carvalho et al. 2018). To facilitate the treatment adherence, tDCS can be used as a home-based technique. While home-based tDCS is the main goal of many recent studies (Castelo-Branco et al. 2020, Pacheco-Barrios et al. 2021, Carvalho et al. 2018, Silva-Filho 2022), it is safe to say that it's an economic and practical adjunctive therapy for patients seeking pain relief when compared to traditional methods (O'Neill et al. 2015). Moreover, studies using more sessions as described by Brietzke et al. 2020 with 60 sessions and Carvalho et al. 2018 using home-based tDCS showed more than 90% of adherence to the sessions, making the portability of this device one of its best advantages.

Can be used as a primer or in combination with other rehabilitation therapies

The optimal treatment for many chronic diseases involves multidisciplinary treatments and physical therapy is usually part of the first line of treatments for chronic pain (Coronado et al. 2017). However, these options are not always completely effective and patients may still suffer with their conditions - due to this researchers tried combining different methods for chronic pain treatment (Şahin et al. 2018). Following this pattern, many papers evaluate tDCS combined with other interventions (Straudi et al. 2018, Beretta et al. 2020, Corrêa et al. 2022, Gunduz and Pacheco-Barrios et al. 2021), usually with positive significant results. Thus, during treatment protocols involving tDCS, patients are usually instructed to continue with their usual care, and tDCS can be combined with other rehabilitative methods, such as physical therapy, as an adjunctive therapy to enhance their treatment sessions.

Cons of tDCS as a therapeutic tool in the rehabilitation of chronic pain

Non-significant to moderate clinical effect sizes and multiple treatment sessions needed to induce long-lasting effects

Several tDCS trials present significant effects: tDCS is useful to reduce pain perception (Pinto et al. 2019). However, the results are still moderate, requiring multiple sessions to reach clinically meaningful outcomes, and in need of optimization of stimulation parameters (Mehta et al., 2015, Lloyd et al., 2020). Some trials even found no significant effects on tDCS for pain (Luedtke et al., 2015). There is a possibility that future clinical trials will find bigger effect sizes, performing longitudinal trials, optimizing parameters, and developing biomarkers of responsiveness, but more studies are needed in order to achieve this goal.

Limited training in centrally-based neuroplasticity treatment options and lack of centers that offer tDCS and training

tDCS is not widely used and has not been adopted in clinical practice, as the treatment option is not currently approved by the FDA in the US. There has been an international panel of research and clinician experts on tDCS who reviewed the research and clinical use of tDCS with findings on how tDCS is currently allocated to research use, off-label treatment, and compassionate use across multiple countries (Fregni et al., 2014). As of 2015 only Soterix Medical and NeuroConn had investigational device exemptions from the FDA (Fregni et al. 2015). Since these devices had to go through sometimes costly regulatory processes, their price is usually higher, leading some researchers or even consumers to seek for cheaper - and non-regulated - market options (Wexler 2015). This situation makes it hard to find specialized inpatient and outpatient centers using tDCS as an alternative means for pain treatment.

History of stigma/prejudice against use of electrical stimulation

Neuromodulatory techniques involving electrical stimulation targeted at areas of the brain can suffer from the prejudice associated with the way electroconvulsive therapy (ECT) is depicted in popular culture. Although tDCS is not ECT, (which, by itself, is performed in a much safer and humanized way today compared to the 1940's and 50's) these misunderstandings still lead some patients to be reluctant or even refuse the therapy. We can only hope that with more information and with the more widespread use of this technique, these misconceptions subside and so does the stigma.

Conclusion

tDCS - and the neuromodulation field as a whole - presents significant positive effects that have greatly improved over the past decade. Many new and ongoing trials are reporting effect sizes that seem to be improving, which may be associated with better knowledge on how to use it. However, some questions

still remain unanswered, so future trials should address these questions.

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