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Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain

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Abstract

Transcranial direct current stimulation (tDCS) modulates spontaneous neuronal activity that can generate long-term neuroplastic changes. tDCS has been used in numerous therapeutic trials showing significant clinical effects especially when combined with other behavioral therapies. One area of intensive tDCS research is chronic pain. Since the initial tDCS trials for chronic pain treatment using current parameters of stimulation, more than 60 clinical trials have been published testing its effects in different pain syndromes. However, as the field moves in the direction of clinical application, several aspects need to be taken into consideration regarding tDCS effectiveness and parameters of stimulation. In this manuscript, we reviewed the evidence of tDCS effects for the treatment of chronic pain and critically analyzed the literature pertaining its safety, efficacy and how to optimize tDCS clinical effects in a therapeutic setting. We discuss optimization of tDCS effects in three different domains: (i) parameters of stimulation; (ii) combination therapies and (iii) subject selection. This article aims to provide insights for the development of future tDCS clinical trials.

Keywords

chronic pain; tDCS; non-invasive brain stimulation; neuroplasticity; neuropathic pain

INTRODUCTION

The management of chronic pain syndromes is currently a challenging task, since only 40-60% of patients experience a favorable outcome from pharmacological treatments[1]. Several studies have shown that the majority of currently available treatments including antidepressants, opioids and topical anesthetics have limited long-term effectiveness and are often associated with moderate, or in some cases, severe adverse effects[2]. One of the main reasons for the lack of efficacy is that current pharmacological approaches have limited or no effect on the mechanisms underlying chronic pain[3–5]. For instance, central sensitization

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is one of the main neural mechanisms associated with chronic pain. Opioid analgesics may increase, rather than decrease, central sensitization[6].

Over the years, alternative therapies such as acupuncture, mirror therapy and thermotherapy, as well as different procedures (i.e. Botox injections) have been performed in an attempt to decrease pain levels. However, behavioral therapies have limited effects on brain plasticity and treatment effectiveness in chronic pain patients. In this context, recent alternative approaches such as neuromodulation techniques have been used not only to alleviate pain but also to revert maladaptive plasticity and may also be used to enhance the effects of behavioral therapies[6].

Transcranial Direct Current Stimulation (tDCS) has significantly advanced in the past 15 years as a treatment tool[7–9]. TDCS has a theoretical advantage when compared with traditional chronic pain treatments since it directly affects central neural targets, thus having a potential stronger effect on central sensitization[10]. On the other hand, its effects may take longer to appear (i.e., only after 5-10 sessions, may subjects notice pain decrease)[11].

The accepted neural mechanism of tDCS is the modulation of spontaneous neuronal firing: decrease or increase according to the polarity of stimulation that results in a change in neural excitability. Cathodal stimulation generally results in reduced excitability (“inhibition”) and anodal stimulation generally results in increased excitability of neurons in the area underneath the tDCS scalp electrodes[12]. The final effect of tDCS depends on parameters of stimulation and also ongoing neural activity[12]. Although all the mechanisms and neural circuits involved with tDCS are not completely known, tDCS of the motor cortex contralateral to the site of pain has been suggested to activate inhibitory systems, thus reducing overactivation of thalamic nuclei[2,13]. Several preliminary studies have demonstrated initial efficacy of tDCS for pain control[7,8,14]. The effects of tDCS on pain control are not limited to cortical structures only as its effects can be seen in the thalamus and also on descending pain control mechanisms[15–17].

Due to its relatively low cost, ease of use and safety profile, tDCS may be a suitable alternative treatment for pain in different disorders[18]. However, as the field moves towards larger clinical trials, new questions arise regarding its effectiveness, safety, methodology and specifically optimal approaches. In this review, we will discuss the current knowledge of tDCS and possible mechanism to enhance its effects for the treatment of chronic pain.

tDCS CURRENT EVIDENCE

Efficacy

The efficacy of tDCS treating chronic pain, including neuropathic pain, has been investigated through multiple clinical trials in the past years[8,9,11,19–28]. In this manuscript, we have reviewed the meta-analyses published in the past 5 years through a PubMed (table 1) database search that estimated the effect sizes of tDCS treatment for pain. Table 1 presents summarized characteristics of the six included meta-analyses in chronic pain conditions, including the subgroups analysis of each one. We excluded two meta-analyses

due to methodological discrepancies related to mean effect size calculation[29,30]. Only the comparison between active and sham groups was included in this analysis.

These meta-analyses included from 2[31] to 16 clinical trials[32] with moderate sample sizes (up to 572 subjects included in the largest meta-analysis); however, for the majority of studies, the sample sizes were relatively small including around 50 subjects[31,33]. Five meta-analyses presented statistically significant results, with the effect size ranging from 0.51 to 1.9[24,31–34]. From these, only one study evaluated the effects of tDCS in overall chronic pain, showing a small effect size and no significant diference[35]. Most of the studies estimated the effects of tDCS in specific chronic pain conditions such as fibromyalgia, migraine, low back pain and spinal cord injury pain. The majority of these meta-analyses have positive results[24,31–34].

Another point to be considered is the large variability between the tDCS protocols, such as differences in electrode placement (M1 or DLPFC) and polarity of the stimulation (anodal or cathodal) that can contribute to the significant heterogeneity between the tDCS trials. Most of the tDCS studies used anodal stimulation over the primary motor cortex (M1 area:C3/C4 – International 10-20 system for the electroencephalography (EEG) electrode) of the hemisphere contralateral to the location of pain (Table 1). Other montages have been tested including anodal/cathodal over the left dorsolateral pre-frontal cortex (DLPFC) for fibromyalgia and migraine[33,34]; and primary visual cortex (V1) for migraine[36–38]. In most of the studies, the cathode was placed over the contralateral supraorbital region.

The majority of clinical trials included in the meta-analyses used protocols with five and 10 consecutive 20-min tDCS sessions (mostly with an intensity of 2mA with an electrode size of 35 cm^2). The analgesic after-effect has been demonstrated to be cumulative and last for 2-6 weeks[8,19,39,40]. Moreover, in the last 2 years, there was a clear trend towards increasing session duration and number of sessions (15 to 20) with a positive impact in pain improvement after the end of the treatment and in the follow up sessions[11,23].

Even though positive results of tDCS on chronic pain have been shown in several studies, to date, clinical recommendation has only been given for two pain conditions: fibromyalgia [level B of evidence (probable efficacy)] and lower limb pain due to spinal cord injury [level C of evidence (possible efficacy)][23].

Therefore, the need for more clinical trials evaluating the effects of tDCS in chronic pain is evident. A better understanding of tDCS mechanism and the standardization of the main parameters are critical for achieving clinical meaningful effects on reducing pain levels. Besides that, so far most of the tDCS clinical trials are phase II studies which have typically small sample sizes and show small to moderate effects on pain levels. There is still a need for phase III pivotal clinical trials evaluating tDCS effects in a larger sample size; however, these studies should take into consideration all the parameters and different population aspects discussed here.

Safety

The Food and Drug Administration (FDA), Health Canada and other international agencies consider tDCS as a non-significant-risk therapy, meaning it is a technique without reasonable expectation of any Serious Adverse Effect[9,18]. A recent review updated the evidence on the safety of tDCS based on the published serious adverse effects seen in human trials and brain damage seen in animal tests. There was no record of serious adverse effects related to repetitive tDCS across more than 32,000 sessions over 1000 subjects using a conventional tDCS protocol: 40 min, 4 milliamperes, 7.2 Coulombs. In animal models, the finding of brain injury by direct current stimulation occurred at intensities over an order of magnitude above that used in conventional tDCS trials[18]. In addition, there have been hundreds of more subjects treated with tDCS that were not analyzed due to unpublished pilot research[41].

Overall, tDCS is a safe technique with adequate tolerability and acceptability. Safety has been tested in several research centers and in different protocols[42–45] which stated that the adverse effects experienced by subjects were mild and slowly disappeared after the tDCS session ended. The latest systematic review published to date reinforced that the most common adverse effects are: mild tingling, burning sensation, itching, transient headaches and skin redness[46]. Recently, authors investigated whether adverse effects become more prevalent and dangerous with increased exposure to tDCS and a larger number of treated subjects. For this analysis, 158 studies (total 4130 participants) were reviewed, taking into consideration tDCS exposure (cumulative charge), revealing that there was no evidence in regards of tDCS as a trigger of maladaptive plasticity or a negative influence for cognitive function[18,47–50]. Moreover, higher cumulative currents were not related to serious adverse effects; however, both erythema and paresthesia were more likely to occur in active conditions as compared to sham[46].

These findings reinforce the notion that tDCS is overall safe and well tolerable in healthy subjects and patients with different conditions[18,47–50]. In the specific case of chronic pain, several sessions of tDCS have proven to be safe in fibromyalgia, spinal cord injury, low back pain and phantom limb pain (PLP)[7,35,43,51,52]. Considering other diagnoses, this technique had no severe harm in epileptic subjects[53,54], or in stroke patients regardless of those with large vessel occlusion[55]. Only transient adverse effects, such mild headache, have been reported. Nevertheless, additional monitoring is required when including these at-risk populations[55]. Pre-existing implants such as metal in the head or neck (e.g., plates or pins) as well as any electronic medical devices in the head or neck (e.g., cochlear implants, vagus nerve stimulator) remain as exclusion criteria for most of clinical trials using tDCS. However, theory based on modeling and limited clinical experience does not show an increase in serious adverse effects in participants with pre-existing implants[18].

Regarding special populations such as children, tDCS treatment for several conditions including: cerebral palsy, encephalitis, and epilepsy have been investigated with no report of serious adverse effects[18]. Nevertheless, there is relatively limited tDCS experience across pediatric populations compared to adults, and extra caution is required. On the other hand, in elderly populations, tDCS proved to be safe and there were no reports of severe adverse events in over 40 studies with more than 600 older adults with a variety of diagnoses[18].

Notwithstanding, the safety of tDCS has been demonstrated primarily for short-term use. So far, to our knowledge, in chronic pain, Castillo-Saavedra et al. tested the longest protocol regimen with 30 consecutive sessions but with a small sample size[11]. This study also showed no evidence of moderate nor severe adverse effects. Further data collection is required to understand the effects of continued tDCS over longer periods[56]. So far, the chronic use of tDCS did not lead to any serious adverse event and some examples to the literature can confirm it: a) a patient with schizophrenia that received two 30 minutes sessions daily over a 3-year period[57]; b) depressive patients that received multiple courses of tDCS (>100 sessions in total)[58] and c) the longest acute treatment trial to date that delivered about six weeks of tDCS, with up to 30 sessions.[59,60].

In summary, the increasing amount of literature on tDCS reinforces its safety and the unlikelihood of it causing serious adverse effects. However, it is important to keep investigating and collecting data on this matter in order to better understand tDCS effects over long term brain plasticity and the manipulation of physical properties of neural tissue.

PERSPECTIVES IN REGARDS OF HOW TO ENHANCE tDCS EFFECTS

As previously discussed, although there is increasing evidence towards the effectiveness of tDCS and preliminary small sample-size phase 2 studies showing positive results for the treatment of different types of neuropathic pain[23], there is a lack of confirmatory trials and the neurological mechanisms involved with its effects are not yet fully ununderstood. Therefore, the definition and understanding of factors that might enhance tDCS effects and how to reach optimum parameters are critical to design pivotal studies.

Combination therapies

Recent studies have been using tDCS as an augmentative type of treatment combining this technique with other pharmacological or behavioral therapies aiming to increase its individual effects; these combinations have been showing promising results. In depression, noninvasive brain stimulation combined with pharmacotherapy has been proven safe and has shown that the combination is more effective in reducing depression symptoms than either of the therapies alone[61,62]. Regarding chronic pain, recent research has been using tDCS as an augmentative type of therapy combined with other techniques aiming to enhance its effect size. To review the current evidence of combining tDCS with other therapies, we systematically searched on PubMed all pain studies that combine tDCS with other therapies (behavioral and pharmacological) in the last 5 years, as to discuss more recent methods of combination. In total, 13 clinical trials and six clinical protocols were identified in several pain conditions and are summarized in Table 2.

A total of 592 subjects were randomized in thirteen clinical trials involving different chronic pain conditions; 4 in low back pain[26,27,63,64]; 2 in fibromyalgia[65,66], 2 in Myofascial Pain Syndrome[67,68], 1 in chronic visceral pain[69], 1 in chronic regional pain (CRPS)[70], 1 in spinal cord injury (SCI)[71], 1 in general neuropathic pain subjects[72] and 4 ongoing studies.[73–77] Most of the studies combined tDCS with a behavioral therapy such as cognitive behavioral training, exercise, visual illusion or with other types of stimulation such as peripheral electrical stimulation (PES) or transcranial pulsed current stimulation (tPCS). Most of the

studies[26,27,65,66,68] showed that the combined group had increased pain reduction effects compared with the control or individual therapies alone.

Mendonça et al. obtained positive and larger effects on pain relief, quality of life, depression and anxiety[65] by combining tDCS with aerobic exercise for the treatment of fibromyalgia when compared with either intervention alone. Using the same rational, 2 other research groups[76,77] are conducting a clinical trials combining tDCS with exercise to treat osteoarthritis pain. In addition, Pinto et al. have been combing tDCS with mirror therapy for the management of phantom limb pain[75]. Moreover, for chronic low back pain (CLBP) the combination between tDCS and PES improved pain, of cortical organization and sensitization, more effectively than when applied alone or compared with the control[26,27,63].

In addition, Kumru and Soler et al. demonstrated that the combination between tDCS and visual illusion can effectively induce significant changes in contact heat-evoked potential (CHEPS), evoked pain and heat pain thresholds[71]. Previously, Soler also demonstrated long lasting effects of tDCS combined with VI in pain relief in patients with spinal cord injury, given that 12 weeks after the end of the intervention the group that received the combined intervention still presented a significant improvement on overall pain intensity, while in the other three groups, no improvement was reported[78].

In this context, mirror therapy and visual feedback seem to be optimal behavioral interventions to be combined with tDCS over M1 since several studies have shown the activation of sensorimotor cortex followed by these interventions[79]. Besides that, previous research indicates that mirror illusion (MI) increases cortical excitability as well[80]. This is an important aspect to be considered while selecting the most appropriate combination therapy, since it is believed that the neurophysiological mechanisms underlying the isolated effects of each treatment tool should point towards similar directions or pathways. Hence, the use of tDCS to enhance the effects of mirror therapy may be a promising treatment for chronic pain disorders such as SCI pain and phantom limb pain[81].

In addition, tDCS over the dorsolateral prefrontal cortex (DLPFC) has been known to enhance cognitive function in both healthy and clinical populations[82]. This can have implications for chronic pain treatment, as this brain area is related to emotional processing and pain, and it is intimately responsible for different cognitive processes such as working memory[82]. In this case, the combined task should recruit the same area to optimize the effects of TDCS. For instance, Powers and collaborators analyzed the effects of tDCS combined with brief cognitive intervention in thermal pain tolerance in healthy controls[83]. The group combining cathodal tDCS (left DLPFC) and brief cognitive intervention showed the largest analgesic effect of all the combinations. In this context, Silva et al. used the Go/No-go Task, which is known for requiring attention and the inhibition of a response according to certain conditions, to modulate distinct attentional networks in fibromyalgia patients[84].

Likewise, tDCS has also been combined with pharmacotherapy. However, in contrary to its use with behavioral therapies, Silva et al. obtained controversial results by using Melatonin combined with tDCS on acute induced pain treatment[72]. In their study, although melatonin

significantly reduced pain, the association with tDCS did not show any additional modulatory effects. However, positive results were also described in children with cerebral palsy. Anodal tDCS over M1 combined with treadmill training led to improvements in static balance and functional performance[85].

In spite of the positive results shown in therapy combination, an important aspect that is still not completely elucidated is which therapy primes which. Either the medications or behavioral therapies can be the ones to prime the effects of tDCS on neuroplasticity and excitability or, in counterpart, the use of noninvasive brain stimulation may the reason why the effects of other interventions (i.e. medication) increase. There is also the possibility of a mutually enhancing effect, in which both interventions would have a complimentary effect on each other. This is important to determine the timing between both interventions, which is sometimes not completely well established. Cabral et al., for instance, investigated whether tDCS should be applied before, during or after motor training[86]. Their data suggested that noninvasive brain stimulation should be applied before, but not after nor during a motor training task to optimize motor learning processes. Hence, the need for more information regarding the relationship between noninvasive brain stimulation, additional therapies and brain pathways is evident.

Understanding tDCS dosage in pain studies

Another strategy used to increase the effectiveness of tDCS is to increase the dosage of the stimulation as to increase its magnitude and duration of after-effects[12]. It is still not fully understood which parameters define the dosage to change magnitude and duration of tDCS studies. We discuss a few parameters that may have such association such as: (1) stimulation intensity (current dosage- amperes); (2) stimulation duration (from 10 up to 30 min) (3) number of sessions (i.e., number of sessions per week) and (4) electrode montage (plus current density)[87].

The potential of tDCS to modify brain excitability parameters has been demonstrated with currents as low as 0.28 A/m^2 [88,89]. Currently most of the tDCS protocols apply 1- 2 mA for a period of 20 to 40 min and have been empirically established as safe over single and multiple sessions. However, an approach to boost tDCS effects is to increase stimulation intensity and current densities, which in theory, leads to a deeper reach of the electrical field and consequently, modulates a different population of neurons.

At the same time, animal studies showed that higher intensity results in enhanced brain modulatory effects without increasing the risk of tissue damage[90]; however, few studies in this regard have been completed in humans. Even though, safety studies in animals provide evidence towards maximal current intensities (threshold in humans, neuroplasticity has non-linear features that need to be considered); therefore, a systematic exploration of the effects of intensity escalation is required[91,92]. Chhatbar and collaborators explored the effects of tDCS dose escalation (1 to 4 mA) showing that a single session of tDCS up to 4 mA for a duration of 30 minutes is safe and has adequate tolerability among ischemic stroke subjects[93]. This is the first evidence demonstrating the safety and tolerability profiles of increased intensity of tDCS stimulation. However, important aspects need to be taken in consideration, including the brain state-dependency from specific conditions.

To date, there are no studies investigating the effects of intensity escalation in neuropathic pain patients, but it is known that at greater intensities, tDCS can cause discomfort and pain and may not necessarily lead to increased clinical effects.

Therefore, another effective approach would be to increase the tDCS session duration instead of increasing the intensity[27,94,95]. A growing body of literature has investigated the effects of short (a few minutes) and long durations of tDCS application of either anodal and/or cathodal tDCS. Short tDCS duration (up to 5 min) resulted in brain excitability modulation only during the application period; in addition, the tDCS after-effects lasted for a short period (max 5 min). On the other hand, longer sessions (above 9 min −13 min) resulted in prolonged after-effects in brain excitability[96]. However, in healthy subjects, it has been shown that longer sessions may induce the opposite effect: a study by Monte e Silva and collaborators showed that 26 min of anodal tDCS (1 mA; M1) results in reduced motor cortex excitability, while shorter durations such as 13 min resulted in the expected enhancement in motor cortex excitability[97]. Controversially, different results are observed for cathodal stimulation (1mA; M1); although 9 min of cathodal stimulation reduced motor cortex excitability, 18 min resulted in the prolongation of the after-effects[98]. However, this effect may be different and needs to be tested in subjects with chronic pain.

Longer-lasting effects are crucial in the attempt of increasing clinical effectiveness; however, only few studies exceeded the usual 20 min of tDCS application duration. Two studies testing 30 minutes of tDCS stimulation for the treatment of chronic pain were performed by (1) Boggio and collaborators[94] and (2) Schabrun and collaborators[27]. In both studies, anodal tDCS was applied over the motor cortex and combined with peripheral stimulation. The combined group showed a decrease in pain perception superior to the effects of tDCS alone. However, there was no comparison of effectiveness within shorter stimulation durations such as the usual 20 min protocol.

Recently, Esmaeilpour and collaborators[99] evaluated tDCS dose-response in different perspectives including computational modeling, human and animal neurophysiology, neuroimaging and behavioral/clinical measures. Overall, the results indicate that the response to the tDCS treatments is not strictly a linear relationship with increasing tDCS intensity (even in the limited range of 1–2mA). Moreover, the nature of tDCS changes in brain excitability are deeply influenced by variations in brain state. Therefore, there is still a need for systematic evaluation of the underlying mechanism by which stimulation duration can be a tool to improve tDCS therapeutic effects for the treatment of chronic pain.

Moreover, factors other than stimulation duration such as the number and frequency of stimulation sessions can also change the duration of the after-effects; consequently, altering the magnitude of tDCS effectiveness. To date, most clinical tDCS studies tested five or more consecutive days of tDCS (once a day)[11,23,100] since multiple sessions are necessary to achieve long lasting modulation of behavioral effects. As an example, a single session of anodal tDCS (2mA, 15 min) over the primary motor cortex induces a selective short-lasting decrease of phantom limb pain in amputees[101]; however, five consecutive days of anodal tDCS (2mA, 15 min, motor cortex) were associated with stronger cumulative effects and

resulted in greater long-lasting relief, up to two months, of both phantom-limb pain and stump pain[28].

The optimal number of sessions and repetition rate to promote and enhance tDCS-induced plasticity effects remains under investigation; recently, authors are focused on more accurately understanding the dosing-calculation required to induce a clinically significant effect. In a recent study, Castillo-Saavedra and collaborators showed that 15 sessions of high definition-tDCS (2 mA; 20 min) is the median number of sessions required to induce a clinically significant decrease of at least 50 % of pain in fibromyalgia patients[11]. Other studies with fewer sessions have shown that conventional tDCS applied over the M1 region is associated with pain relief; however, those effects are still not clinically relevant. Further investigation needs to be performed to understand the optimal number of sessions necessary to induce the largest and longest pain relief, as well as the minimum number of sessions required in order to induce clinically significant effects.

Another important point to increase the duration of the effects of tDCS stimulation is the targeted cortical areas. As discussed in the previous section, brain excitability states vary from different brain areas. For example, working memory studies showed that changing the electrode positioning from DLPFC to M1 abolishes the tDCS effects[82]. In the case of pain, the first report comparing tDCS over the primary motor cortex with DLPFC in fibromyalgia showed that anodal tDCS over M1 was superior to the stimulation in the DLPFC in reducing pain scores[8].

Several studies showed the increased M1 excitability assessed by the increased motor evoked potential (MEP) amplitude after the application of anodal tDCS[96,102–104] and how this M1 excitability increase correlates with pain modulation. However, some other areas of the brain, such as the DLPFC, can be related with additional cognitive aspects of pain[105]. Besides that, recent studies have shown increased M1 corticospinal changes after anodal tDCS over the DLPFC[106]. Moreover, anatomical studies suggested a functional connection between the DLPCF and M1, that could explain the increased levels of M1 excitability after DLPFC stimulation[107–110].

The mechanism underlying M1 excitability changes after DLPFC stimulation are still poorly understood; however, during tDCS, the area under stimulation can induce functional and connectivity changes in the other areas of the brain. Since tDCS physiological changes can modulate local and distant areas of the brain, there is a major importance on the selection of the area that will be stimulated. Despite the latest increase of tDCS research on this topic, there is still a need for studies that systematically assess the optimum doses required to reach clinically significant results, especially in chronic pain.

Subject selection

Our knowledge of enhancing tDCS effects is largely based on limited data; however, recent literature shows the increase of tDCS effects by selecting subjects that can respond better to this type of treatment. One of the most frequent limitations in noninvasive brain stimulation (NIBS) studies is sample heterogeneity, since for most of the studies the severity of the condition can vary significantly, from drug naïve to refractory patients. In the case of pain,

this heterogeneity can be even higher since pain is a self-assessed condition, with large differences in pain thresholds and very subjective upon measurement[111].

A growing body of literature has been dividing subjects as responders and non-responders to NIBS techniques and has recently been trying to identify response predictors to it. A previous study from Nurmiko and collaborators showed that approximately 40 % of the chronic pain patients evaluated responded to high frequency rTMS stimulation achieving at least 20 % of pain reduction[112]. However, the underlying reason for this type of response remains unknown.

Recent evidence suggests that in chronic pain patients, there is an imbalance between excitatory and inhibitory pathways associated with pain response. As an example, fibromyalgia (FM) patients demonstrated a lower conditioned pain modulation (CPM) activity since the rate of FM patients that report pain facilitation during CPM assessments is significantly increased compared with controls (41.7% vs 21.2%)[113]. In this case, there is strong evidence towards an impaired endogenous pain regulatory system in some of the patients with FM. Considering that the CPM efficacy has already been related to pain development 6 months after surgery[114], and that tDCS over the motor cortex enhances CPM responses[115], it could be a suitable marker for response prediction or could be used as selection technique for chronic pain subjects. Consequently, following this theory, the subjects with the highest CPM response (more impairment) should be the ones with higher responses to tDCS[11].

On the other hand, there is also evidence of central nervous system (CNS) alterations in neuropathic pain patients; these changes are associated with a lack of inhibitory control activity, such as decreased short intracortical inhibition (SICI) and facilitation (SICF) and increased resting motor threshold[113]. This inhibitory deficit is associated with altered thalamic anatomy and activity frequently observed in chronic pain patients[116], resulting in abnormal thalamocortical circuits, which explains the association between central pain and thalamic dysrhythmia[117–119].

In this regard, selecting patients with more pronounced alteration in cortical networks involved with pain can be a good strategy to enhance the effects of NIBS treatment[120]. Likewise, changes in motor cortex mapping showed by functional magnetic resonance imaging (fMRI) in amputees were associated with presence and level of phantom limb pain[121,122], and the induction of cortical reorganization by tDCS showed pre-clinical significance for the treatment of this chronic pain. In the same way, EEG changes were correlated with pain levels in fibromyalgia patients[123]. These alterations in neurophysiological outcomes observed in several chronic pain conditions can be used as a tool to better understand the tDCS treatment and select patients that might respond better.

Consequently, selecting patients based on neurophysiological markers - such as TMS assessments of SICI and SICF, EEG and/or MRI- can be an advantage towards the future increase in the effects of tDCS for the treatment of chronic pain. A more accurate understanding of neurophysiological markers for pain onset and response can lead to a transformation in the way pain is treated and diagnosed. An approach based on

neurophysiological changes that takes into consideration brain processes and circuits leads to a better target for treatment; this concept is already being applied in mental disorders by the development of the Research Domain Criteria (RDoC) framework.

Moreover, the level of pain could also be a target to select better responders. As an example, in the case of low back pain (LBP), tDCS combined with peripheral stimulation reduced pain levels and improved high sensory function. However, subjects with more pronounced primary and secondary hyperalgesia responded better to the treatment[26,27].

Similarly, cognitive processes of pain have been used as targets to select and treat patients with chronic pain. In chronic pain, pain catastrophizing is related to the perseverative intrusive thoughts of pain and evaluation of the pain stimuli as threatening[124,125] leading to the enhancement of painful stimuli. High levels of pain catastrophizing are associated with maladaptive cognitive changes[126–131]; for instance in phantom limb pain patients, pain catastrophizing was related to higher stump limb pain and phantom limb pain averages[132,133]. Regarding fibromyalgia, there is a significant association between pain catastrophizing and increased fMRI activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control[134–136]. In this regard, selecting subjects with chronic pain and pain catastrophizing can also be used as an alternative to enhance tDCS effects of overall pain relief. This condition is associated with several brain excitability and connectivity impairments that can respond better to excitability modulation through tDCS.

Therefore, future studies should target the inhibitory deficits underlying pain maintenance mechanisms since reestablishing/resolving the deficits in the regulatory pain system might lead to decrease in pain levels.

Medication interaction

An increased number of studies have tested tDCS to modulate plasticity and cortical networks aiming to decrease chronic pain. However, tDCS effects on neuroplasticity might seem small compared to the big inter-individual variability. In this review, we discussed several options in regards of how to overcome some of these limitations and increase tDCS effects.

Furthermore, a substantial issue that needs to be taken into consideration to better understand tDCS mechanism and improve its efficacy is the interaction between this stimulation technique and pharmacological treatments. In this regard, studies have been showing the acute effects of neurotransmitters enhancing or blocking the tDCS effects on the brain[137,138]. Gamma-aminobutyric acid (GABA)[139], glutamate and other neurotransmitters such as serotonin[140], dopamine[141142], norepinephrine/epinephrine[143], amphetamine[144], acetylcholine[145], nicotine[146–148] and ion channels[149,150]can modulate excitability and consequently alter the tDCS effects and after-effects.

However, most tDCS studies do not discuss the interaction between medication use and effectiveness. In chronic pain clinical practice, most of the patients will be under a long-term

pain medication regimen and this can affect the effects of tDCS stimulation, which can be a problem for the study data interpretation[151]. Therefore, medication interaction and medication screen usage should be systematically assessed in tDCS studies since it can cause excitability enhancement or reduction and change or suppress tDCS modulatory effects.

CONCLUSION

This manuscript reviewed the main aspects of tDCS in chronic pain. TDCS has become a potential candidate for the treatment of chronic pain; however, there is a lack of confirmatory pivotal clinical trials and most pilot-feasibility trials show a small to moderate effect size reducing pain. Besides that, the results of these trials are heterogeneous due to large variability within protocols and parameters as well as between chronic pain subjects. Further work needs to be done to develop optimized protocols to increase its effects sizes. Recent literature describes the advantages of combining tDCS with behavioral therapies such as exercise and mirror therapy. This combination strategy offers a unique perspective combining a top-down strategy (tDCS) with a bottom up intervention (for instance, mirror therapy). The initial clinical trials testing combined interventions as compared to single interventions show positive results. Besides that, the clinical effects of tDCS in chronic pain varies significantly depending on the specific parameters of stimulation, including polarity, size and position of electrodes and number of sessions. In addition, specific population characteristics, such as presence or absence of neurophysiological markers can be a good strategy to enhance tDCS effects and identify better responders. Therefore, choosing optimum doses, patients and the best combination therapies is required to reach clinically significant results, especially in chronic pain. To date, it is still not possible to conclude whether tDCS is associated with a meaningful clinical effect for the treatment of chronic pain. Hence, further studies should explore these mechanisms and better define the optimal protocols to enhance tDCS' effects.

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TABLE 1

Meta-analysis of tDCS in chronic pain.

Author/Date	Clinical Condition	Sample Size	Total Sample Size	Clinical Condition	Group 1	Group 2	Effect Size	P Value
Zhu et al.; 2017[33]	Fibromyalgia	6 studies	168	pain intensity	Anodal tDCS over M1	sham tDCS	pooled SMD for pain was −0.59 (95% CI: −0.90 to −0.27) **	**p = 0.0002**
		2 studies *	48	pain intensity	Cathodal tDCS over M1	sham tDCS	pooled SMD for pain was −0.17 (95% CI: −0.74 to 0.40) **	p > 0.05
		2 studies *	48	pain intensity	Anodal tDCS over DLPFC	sham tDCS	pooled SMD for pain was −0.32 (95% CI: −0.89 to 0.26) **	p = 0.28.
Shirahige et al.;2016[34]	Migraine	6 studies	130	pain intensity	active NIBS (TMS and tDCS; M1 and DLPFC)	sham NIBS	pooled SMD for pain was −0.61 (95% CI: −1.35 to 0.13) **	p = 0.11
		3 studies	78	pain intensity	Cathodal tDCS over visual cortex and anodal tDCS over M1	sham tDCS	pooled SMD for pain was −0.91; (95% CI: −1.79 to −0.03) **	**p = 0.04**
Hou et al.; 2016[32]	Fibromyalgia	16 studies	572	pain intensity	active NIBS (TMS and tDCS; M1 and DLPFC)	sham tDCS	pooled SMD for pain 0.66 (95% CI: 0.44 to 0.88)	**p > 0.001**
		5 studies *	179	pain intensity	tDCS over M1 and DLPFC	sham tDCS	pooled SMD for pain 0.56 (95% CI: 0.26 to 0.87)	**p > 0.001**
Mehta et al.; 2015[21]	SCI pain	5 studies	83	pain intensity	anodal tDCS over M1	sham tDCS	pooled SMD for pain 0.51 (95% CI: 0.11 to 0.90)	**p=0.012**
Boldt et al.;2014[31]	SCI pain	2 studies	57	pain intensity	anodal tDCS over M1 area	sham tDCS	pooled SMD for pain −1.90 (95% CI: −3.48 to −0.33)	**p = 0.018**
O'Connell et al.;2014[28]	Chronic Pain	10 studies	183	pain intensity	anodal tDCS over M1	sham tDCS	pooled SMD for pain −0.18, (95% CI −0.46 to 0.09)	p = 0.19

tDCS: transcranial direct current stimulation; NIBS: non-invasive brain stimulation; TMS: transcranial magnetic stimulation; SMD: standardized mean difference; M1: primary motor area; DLPFC: dorsolateral prefrontal cortex; SO: supraorbital area; VMC: visual motor cortex; SCI: spinal cord injury; ABM: abdutor digiti minimi.

*Subgroups analysis with different sample sizes in the same study (different tDCS montages).

**The negative results favor active tDCS compared to sham for relieving pain.

p= p value; **bold** p values represents significant ones.

TABLE 2

Clinical Trials and Study Protocols Combining tDCS and Other Therapies

Articles Study	Clinical Condition	Study Design	Sample Size	Stimulation Intensity (mA); Electrode Area (cm2)	Anodo	Cathodo	Combination	Groups	Number Of Sessions (Session Duration)	Clinical Outcome	Results
Mendonca et al., 2016[65]	Fibromyalgia	PA	40	2; 35	Left M1 (C3)	Right SO	exercise (E)	Active tDCS + active E; active tDCS + control E; and sham tDCS + active E	5 (20 min)	pain reduction VAS	Pain score reduction: bigger in the active tDCS + active E group
Yoo HB et al.;2017[66]	Fibromyalgia	PA	58	2;35	Left DLPFC (F3	Right DLPFC (F4)	the occipital nerve (ON) stimulation	Sham ON (sham); tDCS on the ON (occipital only); and tDCS on bilateral DLPFC before ON (prefrontal added).	8 (20 min or 40 min group combined)	Fibromyalgia Impact Questionnaire (FIQ) and pain (NRS)	Both groups improved in relation to sham stimulation but prefrontal added group was found to have no additional effect on improving any of the tested measures.
Thibaut A et al; 2017[69]	Chronic Visceral Pain	CO	6	2; 35	Left M1 (C3)	Right SO	tPCS	tPCS +tDCS; 2 tPCS alone; 3 tDCS alone; and sham condition.	1 (20 min)	pain reduction VAS	No difference in pain levels
Schabrun SM et al.; 2017[63]	CLBP	CO	20	1;35	M1 -contralateral to the side of worst pain	SO contralateral to M1	Peripheral electrical stimulation (PES)	Anodal tDCS to M1 + PES to the back muscles; tDCS+ sham PES; sham tDCS+PES; and sham tDCS + sham PES	1 (30min)	Motor cortex mapping (TMS)	Anodal tDCS increased M1 excitability (increased map volume and reduced CSP) in controls but had no effect in the LBP group. PES reduced M1 excitability in both groups. The combined tDCS 1 PES treatment increased M1 excitability in the LBP group but had no effect in controls.
Lagueux et al.;2017[70]	CRPS type I	PA	22	2; 35	M1 (C3 or C4) contralateral to pain leg	SO contralateral to M1	graded motor imagery (GMI)	GMI + active tDCS and GMI + sham tDCS	5 (20 min)	Pain severity (BPI-sf)	No difference in BPI-sf; Group X Time interaction in the subscale measuring pain severity (present pain p=0.046), but not maintained after 1 month post intervention.
Powers A et al.;2017[83]	healthy subjects	PA	79	2; 35	Left DLPFC (F3) or Right shoulder	Left DLPFC (F3) or right shoulder	brief cognitive intervention (BCI); education only as control (PE)	anodal tDCS + (BCI); anodal tDCS +PE;	1 (20 min)	thermal pain tolerance	All groups except anodal tDCS plus pain education evidenced

Articles Study	Clinical Condition	Study Design	Sample Size	Stimulation Intensity (mA); Electrode Area (cm2)	Anodo	Cathodo	Combination	Groups	Number Of Sessions (Session Duration)	Clinical Outcome	Results
								cathodal tDCS + BCI; cathodal tDCS + PE; sham tDCS + BCI; and sham tDCS + PE.			significant analgesic advantages over controls. cathodal tDCS combined with the BCI produced the largest analgesic effect
Hazime FA et al.;2017[23]	CLBP	2×2 FA	92	2;35	C3 or C4 (contralateral to the side of the pain complaint)	SO ipsilateral to the region of pain complaint	peripheral electrical stimulation (PES)	tDCS + PES; tDCS+ sham PES; sham tDCS + real PES; and sham tDCS + sham PES.	12 (20 min)	pain relief, disability and global perception	A two points reduction was achieved only by the tDCS + PES and PES alone. Global perception was improved at four weeks and maintained three months after treatment only with tDCS + PES. None of the treatments improved disability
da Silva NR et al.; 2015[72]	Pain	CO	20	2;35	Left M1	Right SO	Melatonin	tDCS+melatonin; sham tDCS +melatonin; and sham tDCS +placebo melatonin	1 (20 min)	Heat pain threshold	No significant interaction between tDCS and melatonin on HPT
Luedtke et al., 2015[64]	CLBP	PA	135	2;35	Left M1	SO contralateral	Cognitive behavioral management (CB)	active tDCS + CB and sham tDCS + CB	5 (20 min)	Pain intensity (VAS) and disability (Oswestry disability index)	tDCS was ineffective for the reduction of pain and disability
Sakrajai P et al.;2014[67]	Myofascial Pain Syndrome	PA	31	1;35	M1 contralateral to the most painful side	SO contralateral	standard care (SC)	Active tDCS+ SC and sham tDCS +SC	5 (20 min)	Pain intensity (NRS)	Active tDCS group reported significantly more pretreatment to posttreatment reductions in pain intensity that were maintained at 1-week posttreatment, and significant improvement in shoulder adduction PROM at 1-week follow-up than participants assigned to the sham tDCS condition.
Choi YH et al.;2014[68]	Myofascial Pain Syndrome	PA	21	2;35	M1 (C3 or C4) contralateral to pain or DLPFC F3	SO contralateral	Trigger-point injection (TPI)	Active tDCS (M1)+TPI; active tDCS (DLPFC) +TPI and sham tDCS+TPI	5 (20min)	pain reduction	Only in the DLPFC group showed significant change in VAS score between before and after stimulation.

Articles Study	Clinical Condition	Study Design	Sample Size	Stimulation Intensity (mA); Electrode Area (cm2)	Anodo	Cathodo	Combination	Groups	Number Of Sessions (Session Duration)	Clinical Outcome	Results
Schabrun SM et al.; 2014[24]	CLBP	CO	16	1; 35	M1 (C3 or C4) contralateral to pain leg	SO contralateral to M1	peripheral electrical stimulation (PES)	Anodal tDCS + PES; anodal tDCS +sham PES; sham tDCS+PES; and sham tDCS+sham PES.	1 (30 min)	Pain severity (11-point NRS); pain sensitization (PPT); Schober's test and threshold for two-point discrimination (TPD).	Pain severity reduced, on average, by 2.5-2.8 points on the NRS immediately after (until 3 days follow up) all three active interventions (bigger in the tDCS/PES group) but not after the sham intervention. tDCS/PES intervention led to an increased range of motion of forward flexion and PPT increased at the site of pain. TPD reduced and did not differ between the tDCS/PES and PES alone interventions.
Kumru H et al.;2013[71]	SCI	PA	52	2;35	M1 (C3 or C4)	SO contralateral	Visual illusion	tDCS + VI	10 (20 min)	Neuropathic pain intensity	Thirteen patients reported a mean decrease of 50% in the Numeral Rating Scale for neuropathic pain after tDCS + Virtual Illusion
Study protocols											
Luz-Santos C et al.; 2017[76]	OA	2×2 FA	15	2; 5x5cm	M1 (contralateral to the painful knee or the most symptomatic one in case of bilateral pain)	SO contralateral	peripheral electrical stimulation (PES)	anodal tDCS + sham PES; sham tDCS + PES ; sham tDCS + sham PES ; and active anodal tDCS + PES	5 (20min)	pain intensity (VAS) and related function (WOMAC)	NA
Ouellette AL et al.; 2017[73]	CLBP	PA	8	1;35	M1 (contralateral to the side of worst LBP)	SO contralateral (ipsilateral to the side of pain)	Sensorimotor training (SMT)	active tDCS + SMT and sham tDCS + SMT	20 (20 min)	Feasibility and safety	NA
G. Janice Jimenez-Torres et al.;2017[74]	multiple and myriad chronic pain concerns	PA	84	2; 35	Left DLPFC (F3	Right DLPFC (F4)	Standard Care (SC)	active tDCS+SC and sham tDCS +SC	10 (20 min)	pain tolerance and subjective pain experience.	NA
Pinto CB et al.;2016[75]	PLP	2×2 FA	132	2;35	M1 (contralateral to the amputation side)	SO contralateral	Mirror therapy (MT)	tDCS + MT; sham tDCS + MT; tDCS + sham MT; and sham tDCS and sham MT	10 (20 min)	pain reduction (VAS)	NA

Articles Study	Clinical Condition	Study Design	Sample Size	Stimulation Intensity (mA); Electrode Area (cm2)	Anodo	Cathodo	Combination	Groups	Number Of Sessions (Session Duration)	Clinical Outcome	Results
Chang WJ et al.;2015[77]	OA	PA	20	1; 35	M1 (C3 or C4) contralateral to pain leg	SO contralateral to M1	Exercise (E)	active tDCS +E; sham tDCS+E	16 (20min)	pain reduction	NA

tDCS: transcranial direct current stimulation; PA: parallel-arm study; CO: crossover study; M1: primary motor area; DLPFC: dorsolateral prefrontal cortex; SO: supraorbital area; NA: not applicable; VAS: visual analog scale; OA: osteoarthritis; PLP: phantom limb pain; CLBP: chronic low back pain; CRPS: chronic regional pain syndrome; SCI: spinal cord injury; TPI: Trigger-point injection; tPCS: transcranial pulsed current stimulation.