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Methods and strategies of tDCS for the treatment of pain: current status and future directions

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Running Title: Methods and strategies of tDCS on pain

Abstract

Introduction: Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique which has been widely studied for the treatment of chronic pain. It is considered a promising and safe alternative pain therapy. Different targets have been tested, each having their own particular mechanisms for modulating pain perception.

Areas covered: We discuss the current state of the art of tDCS to manage pain and future strategies to optimize tDCS' effects. Current strategies include primary motor cortex tDCS, prefrontal tDCS and tDCS combined with behavioral interventions while future strategies, on the other hand, include high intensity tDCS, transcutaneous Spinal Direct Current Stimulation, cerebellar tDCS, home-based tDCS and tDCS with extended number of sessions.

Expert commentary: It has been shown that the stimulation of the prefrontal and primary motor cortex is efficient for pain reduction while a few other new strategies, such as high intensity tDCS and network-based tDCS, are believed to induce strong neuroplastic effects, although the underlying neural mechanisms still need to be fully uncovered. Hence, conventional tDCS approaches demonstrated promising effects to manage pain and new strategies are under development to enhance tDCS effects and make this approach more easily available by using, for instance, home-based devices.

Keywords: brain stimulation, neuroplasticity, neuromodulation, pain, transcranial direct current stimulation.

Article Highlights

- Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique which has been widely studied for the treatment of chronic pain. Currently, different targets have been tested, each having their own specific mechanisms for modulating pain perception.
- Current strategies include primary motor cortex tDCS, prefrontal tDCS and tDCS combined with behavioural interventions while future strategies, on the other hand, include high intensity tDCS, cerebellar tDCS, home-based tDCS and tDCS with extended number of sessions. Although the underlying neural mechanisms of them still need to be fully uncovered.
- Conventional tDCS approaches demonstrated promising effects to manage pain and new strategies are under development to enhance tDCS effects and make this approach more easily available by using, for instance, home-based devices.

1. Introduction

Transcranial direct current stimulation (tDCS) has been increasingly investigated in the last decades to treat chronic pain [1]. tDCS involves the use of a weak electrical current (approximately 2mA) applied to a specific brain region via two or more electrodes [2,3]. This current induces changes at a subthreshold level, modulating the probability of neural firing when a neuron receives input from another [4]. Anodal tDCS increases the excitability of the underlying cortex, whereas cathodal tDCS decreases it when applied over the primary motor cortex (M1), as measured by transcranial magnetic stimulation [5]. In addition to the short-term effects, tDCS can induce long-term changes at the synaptic level through mechanisms that resemble long-term potentiation (LTP) and depression (LTD) for anodal and cathodal stimulation respectively, leading to an enhancement of neuroplasticity [2,6,7]. It is thought, based on several pharmacological studies that calcium-dependent synaptic plasticity of glutamatergic neurons is underlying the neuroplastic mechanism of action of tDCS since blockade of N-methyl d-aspartate (NMDA) receptors diminishes tDCS effects [8,9]. In addition to excitatory activity, tDCS can also locally reduce gamma-aminobutyric acid (GABA) neurotransmission, and this, regardless of stimulation polarity (anodal or cathodal)[10]. Other biochemical changes have been described, as changes in number and kinetics of ion channels, that could affect the electrical activity propagation and contribute to the non-synaptic plasticity [11,12], ultimately, the direct current could induce water electrolysis and to produce H+ dissociation, showed as increase of pH and synthesis of ATP related to anodal stimulation [13–15]. Moreover, other inflammatory markers as Brain-derived neurotrophic factor (BNDF), β-endorphin, TNF-α, an others; have been described after tDCS stimulation [16–19]. BNDF is a well-known protein correlated with pain and inflammation as it regulates GABA inhibition by membrane co-transporters , therefore, it has been tested in some tDCS studies resulting in a decrease amount of this protein correlated with an increase inhibition and less pain [18] however, it has also been described as a neuroplastic factor related to LTP in chronic pain conditions [20–22] and some studies has propose its use as a biomarker for treatment response [23].

Beyond local effects, connectional effects of tDCS have also been described in neuroimaging studies. tDCS may interfere with functional connectivity, synchronization, and oscillatory activities in various cortical and subcortical networks. This effect has been shown for tDCS delivered to M1[24,25], and to the prefrontal cortex[26]. In healthy subjects under an experimental pain protocol, it has been reported, after an M1 anodal tDCS, an increased fMRI activation of the thalamus, basal ganglia, amygdala, cingulate, precentral, and postcentral areas; on the other hand, cathodal tDCS showed decreased response in the areas [27]. These results demonstrate polarity-specific modulation of tDCS over pain networks [27]. Additionally, M1 anodal tDCS have shown enhance engagement of a descending pain modulatory (DPM) network – specifically in the medial prefrontal cortex, pregenual anterior cingulate cortex, and periaqueductal gray – suggesting that M1-tDCS could reduce the central sensitization-induce hyperalgesia through DPM modulation [28]. Finally, studies with chronic pain populations have shown changes of functional connectivity after M1 anodal tDCS, predominantly reduced connectivity between thalamic ventral lateral nuclei, medial prefrontal cortex, and supplementary motor cortices[29] , suggesting modulatory effects of the pain neuromatrix by tDCS.

Given these neural effects and the possibility to induce them focally, tDCS has been widely studied as an alternative approach to manage pain in various syndromes and pathologies. While pharmacological treatment is the usual therapeutic strategy to manage pain, it presents several disadvantages such as habituation and lack of efficacy, as well as risks of addiction, especially when considering opioids and lack of temporal and spatial focality. In this context, tDCS represents a promising and safe alternative to medication. In chronic pain, most of the significant results come from motor cortex stimulation, as well prefrontal cortex stimulation as an emerging target for chronic

pain treatment [30]. A recent evidence-based guidelines' paper proposed a level B recommendation (probable efficacy) M1 anodal tDCS in fibromyalgia and a level C recommendation (possible efficacy) M1 anodal tDCS in chronic lower limb neuropathic pain secondary to spinal cord lesion [31].

Most common protocols use two electrodes of approximately 25 to 35 cm² and a current intensity of 2 mA. Recently, thanks to the development of computer FEM models and more complex tDCS devices allowing up to 32 stimulating electrodes, high-density tDCS [32] and network-based tDCS [33] protocols have been tested with promising results compared to conventional montages. The development of home-based devices is assumed to be determinant for the clinical translation of tDCS as it overcomes the issue of patients' travel to a research institution or hospital and therefore, high rate of drop-outs [34,35]. Increase in current intensity thought to induce strong neuroplastic effects has also been tested without causing any significant side effects [36].

In this article, we will, therefore, review different strategies of tDCS for chronic pain. We divided in two main section: current and future strategies. For the current strategies, we will review: Primary motor cortex tDCS, prefrontal tDCS and tDCS combined with behavioral interventions. For future strategies we reviewed: high-intensity tDCS, cerebellar tDCS, home-based tDCS, tDCS to prevent pain and tDCS with extended number of sessions. We defined current vs. future on the amount of preliminary data. As the goal of this review is to discuss strategies rather than summarizing the evidence and providing effect sizes of different strategies, we only discuss a few articles in each strategy as an example.

2. Current Strategies

2.1. Primary motor cortex (M1) tDCS

The rationale behind using motor cortex stimulation to reduce pain relies not only on the connection between motor cortex and the thalamus but also on the communication with other structures as the brainstem, cingulate gyrus, prefrontal cortex and insula [37–40]. These powerful connections might inhibit the nociceptive signal decreasing pain perception. Moreover, there are other pathways related to pain control, as the disinhibition of the periaqueductal gray leading to an enhancement of the endogenous pain modulation system by the connection with the dorsal horn at the spinal cord [41]. Another important factor is the current state of neural network, priming the network to enhance a specific result has been studied in different motor cortex stimulation techniques and given that tDCS delivers a subthreshold current, this approach should be beneficial when it is combined with another behavioural technique [42,43]. Anodal M1 tDCS works as a top-down regulation sending signals towards the thalamo-cortical connections, prefrontal cortex, cingulate gyrus and the periaqueductal gray [39,44,45]. Based on this assumption, Lang et al. (2005) [46] reported a significant activation of cortical and subcortical in pain related areas with anodal stimulation. Furthermore, two studies using tDCS describe an increase of endogenous opioid release in the thalamus, insula, cingulate, and nucleus accumbens. Moreover, pre-clinical and clinical studies have found changes on inflammatory cytokines [16–19]. Suchting et al. (2019)[16] described a decrease of serum TNF-α, β-endorphin, IL-6 and IL-10 after 5 sessions of M1 tDCS in patients with knee osteoarthritis. Indeed the motor cortex seems not to be only a passive target, but it is actively involved in the modulation of pain networks as its activity is also modified in subjects with chronic pain [47]. These studies support the idea that anodal M1 tDCS would be a successful target for pain control.

Over the last years, clinical studies targeting anodal M1 for pain control have had significant results. Different conditions have been considered as fibromyalgia [17,48–57], neuropathic pain[58–70], migraine[71–76], low back pain (LBP)[77–81], musculoskeletal conditions [16,82–87],

myofascial pain syndrome[88,89], post-operative pain[90–93], among others (See Table 1). Fregni et al. (2006)[64] was one of the first clinical trials using this approach in neuropathic pain due to spinal cord injury, using 5 sessions of anodal m1 tDCS. This target decreased more than 50% of the initial pain score compare to the sham group. Whereas Khedr et al. 2017 [17] studied 40 patients with fibromyalgia, obtaining a significant decrease of pain perception after 10 sessions of anodal M1 tDCS with a moderate effect size and a significant increase of β-endorphin. As tDCS is a subthreshold stimulation, anodal M1 prime the adjacent neural networks when associate to an adjuvant therapy as demonstrated by Boggio et al. (2009) [60] using tDCS with TENS for chronic pain, Soler et al. (2010) [62] combining tDCS and visual illusion therapy, Riberto et al. (2011)[56] and Mendonca et al. (2016)[57] used tDCS with a multidisciplinary program and aerobic exercise, respectively, for fibromyalgia in order to enhance the DPM network. However, due to the different conditions and the variability of stimulation parameters, the interpretation of effect sizes should be carefully discussed. One of the largest study using M1 as a target for chronic pain is the study of Luedtke et al. (2015)[79] with 135 non-specific chronic low back pain participants. The non-significant results might be related to the combination of anodal M1 and cognitive-behavioural therapy, activating different and potentially opposites neural networks. Whereas, Straudi et al. (2018)[78] combined anodal M1 with exercise, decreasing significantly three times more the pain score compared to sham tDCS in chronic low pain population; and Jafarzadeh et al (2019) [80] combined anodal M1 with postural training achieving a significant decrease of pain score after 6 sessions and after one month of the stimulation. On the other hand, for some conditions, the location of the anode and the cathode still debatable. In migraine patients, anodal M1 tDCS have reported significant results [71,73,74] as well as cathodal M1 stimulation[74], however, there is evidence of other targets as anodal and cathodal over sensory cortex [94] and cathodal in the visual area [95–97]. More comparative studies are needed to disentangle the question on the better stimulation localization.

The length of the treatment is also variable among conditions. In fibromyalgia, studies of ten session (five per week for two weeks) have had significant decrease of pain compare to ten sessions (once a week for two weeks). Moreover, Valle et al. [53] had significant results even after two months follow-up after ten sessions of tDCS. In neuropathic pain, Soler et al. [62] combined tDCS with visual illusion having significant decrease of pain after the ten sessions (five per week for two weeks) and lasting after 12 weeks of follow-up. On the other side, studies of five or less sessions have variable results. Migraine studies have had a greater number of sessions, from ten up to 22 sessions of tDCS. Auvichayapat et al. [71] after 20 sessions had significant decrease of pain after treatment and up to eight weeks after while Dawood Rahimi et al. [75] with 22 cathodal tDCS sessions significantly decreased pain frequency, duration and intensity. Other musculoskeletal pain conditions as osteoarthrosis and LBP, five to ten sessions combined with a therapy have had significant results lasting up to one month. Other studies are currently developing innovative RCTs for chronic pain as fibromyalgia, Castelo et al. [98] with 18 sessions of anodal M1 tDCS combined with aerobic exercise (five sessions per week for two weeks follow by three sessions per week for two more weeks as a maintenance) with a 3-month follow-up period.

We can conclude that anodal M1 tDCS has been a successful target for chronic pain management as highlighted in a recent meta-analyses.[31]. Therefore, choosing the right intervention with the right target it is important for a synergistic effect. Nonetheless, there is a need for more studies with larger sample with neurophysiological and biological outcomes to support this theory and further understand the mechanism of pain reduction with motor cortex stimulation.

2.2. Prefrontal tDCS

Pain perception is controlled by a complex network of brain regions and circuits, which are referred as the *pain matrix* [99–101] – and involve cognitive, emotional, and affective components. The dorsolateral (DLPFC) and medial prefrontal cortex (mPFC) are important areas involved in pain perception[102,103]. . They also contribute to the cognitive process of experiencing pain, especially related to pain prediction, evaluation and reinterpretation [104]. Thus, neuromodulation interventions targeting the prefrontal cortex have been investigated to reduce pain by acting on its cognitive component.

Neuroimaging studies suggest that reduction in pain levels following the stimulation of the prefrontal cortex could be due to connectivity between this region and other pain perception areas such as the cingulate cortex, the insula, the amygdala, and the thalamus[102].There is evidence that painful stimuli produce an activation pattern on the DLPFC suggesting an essential role in the interpretation of the painful stimulus [105]. Besides, tDCS studies targeting the DLPFC showed to modulate subcortical structures, which may influence the emotional and motivational aspects of pain[106,107]. One hypothesis is that in chronic pain conditions the maladaptive neuroplasticity produce an unbalance attentional and cognitive resources allocation producing a misperception of pain, and the DLPFC could have a role in this maladaptive resources allocation [106], thus, excitatory stimulation of DLPFC in chronic pain patients could lead to an inhibition of this maladaptive cognitive and attentional resources allocation drives to a reduction of pain. According with this hypothesis, there is evidence about DLPFC role in pain suppression, pain detection, pain sensitization and pain coping [106,108–110]. Some studies highlighted an activation of the DLPFC bilaterally, but predominantly left, following pain suppression during acute pain stimulation, and unpleasantness reduction of thermal pain [103,111] suggesting that left DLPFC is an adequate stimulation target. Also, the connectivity among left and right DLPFC is associated with individual pain perception; stronger interhemispheric connectivity results in greater pain tolerance[112], suggesting that bifrontal stimulations could also have an effect on pain modulation.

Several clinical trials are testing prefrontal tDCS stimulation for treating pain (See Table 1)[113]. The most current montage is anodal stimulation over the left DLPFC [31]. There is evidence that this stimulation influences the affective component of pain processing and that the activation of this region may reduce overall pain sensation [99]. Boggio et al. showed that DLPFC stimulation leads to a decrease in pain perception[102,114]. Interestingly, the DLPFC stimulation showed an increase in pain empathy [115]. These findings corroborate that DLPFC influences the cognitive-affective appraisal of pain experience and thus support this as a stimulation target for pain reduction. However, the effects of DLPFC stimulation seems to be dependent on pain syndromes, especially for those with cognitive-affective dysfunction such as subjects with high catastrophizing [116] or fibromyalgia [23,117].

Clinical trials in fibromyalgia patients showed significant pain reductions of anodal left DLPFC stimulation. Brietzke et al. (2019) [23]showed that a 60 sessions over 12 weeks of home-based tDCS reduced 62.05% of the cumulative pain scores compared to sham and reduce the risk of analgesic use in 55%. To et al. (2017) [117] evaluate the effect of bifrontal tDCS stimulation showing significant results on pain and fatigue improvement in fibromyalgia patients. Using a bilateral montage of anodal in the left DLPFC and cathode on the right DLPFC. However, these effects are not superior to motor cortex tDCS stimulation to reduce pain, as it was showed by Fregni et al. (2006)[49] in fibromyalgia patients, but, the involvement of left DLPFC has been highly associated with cognitive-affective pain controllability in these patients.

In conclusion, prefrontal tDCS stimulation is a promising target to improve cognitive and emotional aspects of pain. Clinical trials studying the mechanisms of action and connectivity between

the prefrontal cortex and subcortical areas are critical to select the best stimulation parameters and enhance tDCS-related analgesic effects.

2.3. TDCS combined with behavioural interventions

Given the mechanisms of action of tDCS, combination therapy to enhance neural activity in the stimulated area has been widely investigated. In fact, one of the most challenging tasks when trying to optimize pain management is being able to target and ultimately modulate basic and yet unclear neural mechanisms associated with chronic pain. Central sensitization, for instance, represents one of these important mechanisms [118]. While pharmacotherapy, such as opioid analgesics, may increase rather than decrease central sensitization [119], which may even worsen the pain; tDCS mechanisms seem to induce activation in other neural circuits that ultimately can induce inhibition in pain-related circuits, thus reverting maladaptive plasticity [118]. In addition, it has been suggested that tDCS alters sodium and calcium channels as well as NDMA-receptors' activity. Thus, it generates stronger effects on central sensitization and potentially decreases pain levels.

Like tDCS, behavioural therapies have also been proven effective for pain reduction and may also be associated with the mechanisms discussed [120]. In fact behavioural training may enhance activation in circuits primed by tDCS enhancing its plastic effects [118]. Consequently, it is possible to observe the activation of sensorimotor cortex depending on both type and duration of the behavioural intervention [121]. However, based on its limited effects on brain modulation and maladaptive plasticity, one of the most important disadvantages of behavioural interventions is its short-term pain reduction, thus requiring multiple sessions and longer periods of treatment, and, as every intervention tested so far, its incapability to promote a complete recovery as a single therapy [30]. Therefore, several studies have been aiming to enhance the effects of non-invasive brain stimulation and behavioural therapy, by combining both interventions and their synergistic mechanisms on pain reduction.

Pinto et al. [118], for instance, described a total of thirteen clinical trials investigating the combination between tDCS and behavioural therapy for conditions such as low back pain, fibromyalgia, chronic visceral pain, chronic regional pain, myofascial pain syndrome, and chronic pain due to spinal cord injury. However, despite the amount of existent information on this topic, the therapeutic application of combined therapies is still not standardized and requires further investigation.

For conditions as *neuropathic pain* some strategies has been proposed as the combination of tDCS with TENS, a Breathing-controlled electrical stimulation to the median nerve or visual illusion. In a double-blind, placebo-controlled trial, Soler et al randomized 39 patients into four groups: transcranial DCS + visual illusion group, transcranial DCS + control illusion (transcranial DCS group), transcranial DCS sham + visual illusion (visual illusion group) and transcranial DCS sham + control illusion (placebo group)[62]. Each patient received ten treatment sessions during two consecutive weeks in order to test the theory that the beneficial effects of transcranial DCS and movement illusions might be synergistic [62]. As a result, they were able to demonstrate that the combination between tDCS and VI can be effective in the management of neuropathic pain following spinal cord injury. Also, the benefits of this combined intervention were more significant and longer lasting than each intervention individually [62]. Therefore, they were able to observe the effectiveness of combining tDCS and behavioural therapies for pain reduction.

Moreover, in other neuropathic pain conditions as *phantom limb pain* strategies involving visual feedback have become an important alternative therapeutic option for pain relief, this attempts to correct the incongruence between motor output and sensory feedback, which is suggested to be intimately related with chronic pain [62],. Over the years, researchers have observed that a reduction

of pain levels may be achieved as a result of the visual input generated by the paralyzed/missing limb during movement, which reverses sensory-motor mismatch and normalizes cortical somatosensory representation maps [122]. Mirror Therapy (MT), for instance, as well as the use of movement imagery and visual illusion, have shown positive results for a number of chronic pain conditions [123–126]. It has been proposed that by observing the reflection of the movements performed by the intact limb, the individual is able to create visual feedback, thus activating neural pathways and consequently compensating the absence of sensory input in case of an amputation, for instance [127]. However, the effects of these beneficial changes on pain levels demand multiple sessions of mirror therapy over the course of several weeks and there usually is a large variation in treatment response among patients, which can be related to demographic characteristics, such as gender, pain intensity and type of pain [128]. Also, patients' perception of the distortions in the affected limb might influence their ability to relate with the visual reflection and to develop a sense of ownership, aspects that are fundamental predictors of treatment success [129]. Visual illusion (VI), on the other hand, might overcome some of these limitations faced by mirror therapy. As this technique consists in replacing the representation of the affected limb by a computer-generated graphic representation, it is able to recreate patients' individual and unique characteristics [130], increasing similarity and vividness as a consequence. Furthermore, advanced setups may also contribute to other aspects such as the control of the artificial limb via electromyography and the potential to add game elements in order to facilitate treatment adherence. Despite these advantages, visual illusion application demands high technical requirements, financial support, and is still not widely available.

In addition, Lira et al tested the effects of anodal, cathodal and sham tDCS on the posterior parietal cortex or on the premotor cortex during Rubber Hand Illusion (RHI) in 156 patients [131]. By quantifying RHI in (1) onset time for the feeling of body ownership of the rubber hand, (2) proprioceptive drift, and (3) questionnaire about the intensity of the illusion as reported by the participant, they were able to observe that anodal tDCS decreased illusion onset time and the subjective experience of body ownership [131]. Therefore, their study suggests that, besides accelerating the time to integrate an artificial body part, tDCS also increases the perception of body ownership. These studies thus provide important evidence that this combination results not only in pain improvement but also in enhancement in sensorimotor plasticity. Hence, further studies are crucial for the validation of these combined interventions as a possible therapeutic approach for chronic pain.

For other conditions as *fibromyalgia,* a tentative combination of exercise and tDCS has been suggested. Aerobic exercise (AE) acts systemically, thus influencing several aspects of body function by affecting large neural circuits via afferent input (bottom-up) due to somatosensory stimulation and neuroendocrine responses [57]. Also, AE can alter brain activity through motor cortex activation and neurotransmitter release, concept known as exercise-induced hypoalgesia [132]. This type of activity has the advantage of being easily sustained by the patient afterwards, maintaining and boosting the acquired improvements [133]. Mendonça et al. (2016)[57]evaluated 45 patients who suffered from fibromyalgia and were divided in three groups (active tDCS + active AE; active AE + sham tDCS; Sham AE + active tDCS) to assess whether the group that received both active interventions would demonstrate greater pain reduction. After performing aerobic exercise on a treadmill over one month, the three groups presented no differences regarding motor cortex plasticity. Nevertheless, the combination between tDCS and aerobic exercise was superior compared with each individual intervention (Cohen's d effect sizes > 0.55), also demonstrating a significant effect on pain, anxiety and mood [57]. Finally, it is important to notice that, according to Fregni et al (2006)[49], the continued use of tDCS can lead to pain relief for 1 month after the end of the intervention as a result

of induced plastic changes. Therefore, it is possible to assume that the combination between tDCS and aerobic exercise might generate results with an even longer duration.

Physical exercise combined with tDCS is also being tested for patients presenting knee OA [134]. Immediately after sham or active tDCS, 20 patients performed a standardized 30-minute set of quadriceps strengthening exercises for 8 weeks, as to analyse whether tDCS enhances the effects of physical exercise or not for this specific population obtaining decrease of pain and improving physical function [134,135]. In a recent metanalysis, a moderate effect size was found in the combination of tDCS and exercise for chronic pain compare to tDCS alone [136]. Another approach is the synergistic effect of meditation and tDCS. Ahn et al. (2019) have recently tested the combination between home-based tDCS and mindfulness-based meditation for pain in patients with knee OA [85]. In this study, thirty patients with symptomatic knee OA were randomly distributed among two groups to receive either 10 daily sessions of home-based 2 mA tDCS paired with active MBM for 20 min or both sham tDCS and MBM. By using a Numeric Rating Scale (NRS) and Western Ontario and McMaster Universities Osteoarthritis Index, they were able to notice a significant reduction of pain scores in the active tDCS paired with active MBM group, as well as increased pressure pain thresholds and conditioned pain modulation [85]. These findings demonstrate promising benefits for OA patients and encourage the development of new studies for other conditions along with the exploration of Yoga benefits, given that no studies involving this intervention combined with tDCS have been concluded so far.

Regarding *chronic low back pain*, recent guidelines have recommended a multidisciplinary approach as an effective tool for symptoms relief [137]. Accordingly, tDCS has been associated with group exercise, which, in this study, includes posture advisement as well as muscle stabilization and mobilization exercises for the trunk with a one hour duration (2-3 times /week) for a month [78]. Their results showed that, when combined with group exercise, real-tDCS may induce larger effects on pain and psychological well-being [78]. Another therapeutic approach being tested in combination with tDCS is sensorimotor retraining, a novel treatment that consists on motor control exercise and lumbar tactile retraining [138]. Sensorimotor retraining's mechanisms involve the modulation of motor and sensory cortical changes in conjunction with the improvement of neural systems related with pain [139]. Most studies on the combination between this intervention with tDCS, however, are still preliminary or in the initial stages. The study from Ouellette et al, for example, is a protocol for a pilot randomized controlled trial [140]. In summary, despite the initial positive results, it is still unclear the type and intensity of physical exercise to associate with tDCS.

3. Future Strategies

3.1. High-Intensity tDCS

The majority of tDCS studies on pain has tested the effects of weak electrical currents, mostly exploring current intensities between 1 mA and 2,5 mA [141]. Despite the beneficial therapeutic effects of weak current tDCS on chronic pain alleviation, it has been proposed that higher intensity tDCS, ranging from 3 mA to 4 mA, could promote brain modulation in a superior way [142]. Such higher intensity protocols were avoided due to a concern of investigators regarding possible brain tissue damage. As to adequately comprehend these potential effects, also its impact on subcortical brain structures, a few studies on the mechanisms of high-intensity tDCS have been conducted [143,144].

There is evidence that higher intensity tDCS may progressively decrease body resistance along with its application [144]. As the current intensity is turned up, the body or scalp resistance is diminished. This is in line with the report of a recently published study of high-intensity tDCS on stroke patients, which has shown that high current stimulation may provide greater changes in body

resistance [36,143]. It is also accepted that the electric field induced in the brain may increase linearly with the applied current through tDCS [145]. This fact may justify a potential benefit of higher current tDCS on the treatment of pain, although efficacy studies with this type of protocol have not been conducted. Furthermore, it is known that tDCS may generate an electric field that reaches deep areas of the brain, not only superficial regions as previously believed [141]. Thus, this is another aspect which higher intensity tDCS may influence, with a potential to promote greater clinical effects than stimulation using lower intensities.

The rationale for using tDCS with higher intensity is to reach deeper areas associated with pain processing. Such areas would be the cingulate gyrus, the insula, and thalamic nuclei. Studies with invasive brain stimulation targeting these areas have shown significant effects [103,146]. Another reason may be related to the larger effects of motor cortex stimulation with invasive stimulation that provides higher intensity currents [147]; thus even considering the motor cortex, tDCS with higher intensities may be associated with larger effects. Finally, in older subjects with chronic pain such as osteoarthritis, this should also be useful as due to brain atrophy the scalp-brain distance is higher thus more current may be needed to reach the same cortical areas [148,149].

Current studies on high-intensity tDCS are still testing the safety of this technique, which explains the fact that it has not yet been tested as a therapeutic method for the treatment of pain. Despite the lack of reports, a recent clinical trial on healthy adults has provided evidence in support for the tolerability of 4mA tDCS [142]. They found no significant difference in pain scores or adverse events between groups receiving electric current of 2mA and 4mA. If safety is confirmed with this approach, efficacy trials of high-intensity tDCS on pain control are required to explore improvements in clinical outcomes.

3.2. Home-based tDCS

An important limitation in translating tDCS to clinical practice despite the positive results to date is the need to receive tDCS in a research centre. However, recent studies have started to assess tDCS effectiveness at home. In a recent study in fibromyalgia, it has been shown that an extended period of tDCS 2 mA (60 sessions at home across 12 weeks) self-applied using a customized tDCS device targeting the DLPFC induced an improvement in pain scores with a large effect size (ES=1.59) and enhanced depressive symptoms, catastrophizing due to pain, and reduced the analgesic use [23]. Another unblinded randomized pilot study tested the combining home-based tDCS with mindfulness-based meditation for pain in older adults with knee osteoarthritis assigned to receive 10 daily sessions of home-based 2 mA for 20 min. They found that active tDCS paired with active meditation significantly reduced pain scores, increased pressure pain thresholds, and the conditioned pain modulation [83]. A study with 12 consecutive patients neuropathic pain refractory received by wireless (Bluetooth) connection between the stimulator and mini-laptop daily tDCS sessions during 5 weeks in a double-blinded, sham-controlled trial. Active-tDCS 1.5 to 2 mA for 20 min was applied over M1 and cathodal over the frontopolar region contralateral to the anode. They rated daily pain daily during 11 consecutive weeks, and afterward via iterative visits/phone contacts. Patients achieved satisfactory relief on a scale combining pain scores, drug intake, and quality of life [150]. In another randomized study, we evaluate the feasibility of tDCS at home for 10 days (10 sessions) in 20 healthy subjects (8 men /12 women). We measured adherence by counting the number of completed courses, as verified by the records on the software, and we found 90% of adherence to the proposed sessions[151]. In the same study, eight fibromyalgia patients used an extended period of tDCS (60 courses across 12 weeks), and the adhesion was 94% [23]. In a current randomized in parallel double-blinded design, with adults' females with fibromyalgia allocated 2:1 to receive a-tDCS or sham tDCS for four weeks (20 sessions) we found that the adherence verified by the records on the software in the

active-tDCS was 91.71% (n=28), while that received sham-tDCS was 98.51%(n=14) [152]. In addition, the studies with tDCS at home have found only minor adverse effects with an incidence comparable to the ones described in the literature when the treatment is applied under direct supervision [23,150,151].

To date, to receive this treatment, patients need to commute daily to the specialized centres, which disrupts their commitments and this factor also increases healthcare's cost. However, given the current COVID-19 situation, chronic pain population has been affected in receiving treatment and increasing pain from external factors stress and anxiety [153]. Brocalero-Camacho et al. (2020)[154] explains the effects of discontinue tDCS sessions in chronic pain patients, highlighting the importance of a potential home-based therapy. For a safe treatment with tDCS at home, the device needs to present some safety characteristics, such as for example, a blocked system to guarantee the dosage and prevent overuse. In addition, it is essential that users cannot change electrode positions, and the device software should register the impedance contact and interrupts the session if the impedance exceeds a value determined. In addition, ideal equipment for home-based tDCS at home needs to track the time that current circulated between the electrodes to assess the adhesion to treatment. The equipment needs to be an easy handle-device to self-application to permit flexible schedule to apply the therapy according to the personal schedule. Above all, the device should be tested in studies with good methodological quality to guarantee that the tool offers effective treatment. It needs to stress that this therapy approach should be prescribed by a health professional with knowledge on neurobiological processes and based on medical diagnosis to guarantee the best stimulation parameters and the appropriate areas to be stimulated.

3.3. Cerebellar tDCS

Chronic pain conditions are associated with maladaptive plasticity changes in the nervous system producing an imbalance among excitatory and descending inhibitory pathways[155,156] . Different anatomical and functional areas are involved in this process [157]. Recently, some studies have suggested that the cerebellum may exert a key role in the sensory-motor integration related to analgesic process[158] and in behavioral responses to nociceptive stimulation. These findings suggest the cerebellum could be a useful brain stimulation target for pain management [157].

Some studies showed that cerebellar tDCS (c-tDCS) modulates pain perception in humans, probably by interfering with the inhibitory tone exerted by the cerebellum over cortical areas – the cerebellar brain inhibition [159,160]. The cerebellar brain inhibition pathway is an inhibitory output from the cerebellar cortex (mainly Purkinje cells) through the cerebellar nuclei, which subsequently relayed to the cortex via the thalamus where they project to several areas, including prefrontal, anterior cingulate and sensory-motor cortices[161], demonstrated using a TMS protocol (an excitatory pulse in the cerebellum produce an inhibition on the motor cortex response) (111). Since the cortico-thalamic connectivity and sensory-motor cortices in chronic pain conditions are less inhibited (reduced GABAergic tone)[142], the excitatory cerebellar stimulation could restore the inhibition due to a cerebellar brain inhibition enhancement[163,164] and reduce pain. According to this hypothesis the modulation of cerebellar brain inhibition using non-invasive brain stimulation techniques in chronic pain syndromes, seems to interfere with maladaptive motor patterns, promoting motor skills acquisition, and reducing pain perception.

A quasi-experimental study [165] and a randomized clinical trial [166] (see table 1) used this target stimulation to evaluate pain-related outcomes. Bocci et al. 2015 [167] found that cerebellar tDCS modulates pain perception and its cortical correlates in healthy subjects – anodal polarization decreases the perceptive threshold and decreases the visual analog scale score, while the cathodal having the opposite effects. Pereira et al. 2017 [160] evaluated the effect of anodal c-tDCS modulates

lower extremity pain perception in healthy volunteers, showing an increase of pain threshold of the ipsilateral leg.

Moreover, Bocci et al. 2019 [166], performed a double-blind sham-controlled crossover trial in fourteen patients with phantom limb pain (upper and lower limb amputees, mixed etiologies), showed that anodal c-tDCS improves both paroxysmal pain and non-painful phantom limb sensations in subjects with upper limb amputations, but no changes in phantom limb pain and stump pain intensity. The main limitations in these studies are the small sample size and the variability of the reference electrode (buccinator area versus right shoulder), which can modify the electrical current direction and the final stimulation target. Also, it is necessary to explore the combination of c-tDCS with more studied behavioral interventions (e.g., mirror therapy, motor imagery) ([167], since it has been reported synergic effects of tDCS and behavioral interventions to reduce pain (79).

The mentioned findings prompt research of the anodal cerebellar DCS as a possible novel and safe therapeutic tool in chronic pain patients, but well-powered RCTs with standardized stimulation parameters are needed.

3.4. Transcutaneous Spinal Direct Current Stimulation (tsDCS)

A new potential application of electrical stimulation of the central nervous system is the spinal application of DCS. It is defined as transcutaneous spinal direct current stimulation (ts-DCS) and it is considered as a non-invasive, safe, non-pharmacological and potentially self-administered approach to those conditions where pain is generated or perpetuated through changes in spinal cord interneurons.

Modelling studies [168] have showed a direct and longitudinal current density and electric field along the spinal cord, suggesting a feasible transcutaneous stimulation of multiple spinal cord segments. From preclinical studies, anodal ts-DCS has been proven to inhibit nociceptive responses, such as the nociceptive withdrawal reflex [169], the NWR temporal summation threshold [170], and laser-evoked potential amplitude[171]. The hypothesized mechanism involved in this modulation could be a direct or supraspinal-mediated change in excitability (NMDA-mediated plasticity) of spinal sensory neurons, including the wide dynamic range (WDR) neurons, which are involved in the spinal cord pain processing as well as in and the genesis and maintenance of chronic pain [170]. In summary, tsDCS could modulate neuronal activity in lemniscal, spinothalamic, and segmental spinal circuits, by glutamatergic system involvement, and ultimately modifying spinal cord plasticity [172] .

The majority of previous studies have demonstrated a local and segmental effects; however, Truini et al. (2004) suggested that anodal tsDCS reduces the amplitude of N2 component of the laser-evoked potential, which represent a disengagement of anterior cingulate cortex, thalamus, and posterior insula, which are regions involved in pain perception, therefore suggesting a cortical effects of anodal tsDCS [171]. Although, more studies are needed to understand the mechanism of action of tsDCS in chronic pain populations.

Regarding pain outcomes, Meyer-Frießem et al. (2015) reported in healthy subjects that anodal tsDCS may reduce painful reflexes and may be associated with analgesic effects [173]. Compared to other neuromodulation techniques, only two RCTs have assessed the effects of tsDCS in chronic pain conditions [174,175] (See table 1). One study included 10 subjects with cervical traumatic SCI experiencing neuropathic pain ant tested one session of anodal thoracic spinal cord stimulation [175]. The authors reported no difference in pain intensity between the active and sham tsDCS groups. However, the small sample size, the lack of consecutive sessions, and the inclusion of patients with long injury duration (mean of 8.9 years), prevent a meaningful interpretation. Another

study on multiple sclerosis patients (n=33) with central neuropathic pain found a significant and persistent (1 month after treatment) pain reduction after 10 daily sessions (anodal thoracic spinal cord stimulation)[174].

The mentioned findings encourage research on anodal tsDCS for pain management as a possible novel and safe option, but well-powered RCTs with standardized stimulation parameters and consecutive sessions are needed before any translation to clinical practice could be done.

3.5. TDCS to prevent pain

Some chronic pain conditions are preceded by an acute pain event. This is related to a decrease in quality of life, morbidity, mortality, and an increase of opioid intake. Different treatments have been studied to prevent pain; however, the efficacy still debatable [176]. One possible target is to enhance the endogenous pain modulation system before pain arises. The endogenous pain modulation system in healthy population and acute pain conditions have the ability to deal with nociceptor stimuli via supraspinal structures as primary motor and sensory cortices, the thalamus, the cingulate cortex, the periaqueductal gray, the rostral ventromedial medulla and the connection with the subnucleus reticularis dorsalis and projections to the spinal cord [177–181]. However, this pathway is impaired in chronic pain leading to an unbalance on the endogenous pain pathway. This impairment can be measured by the conditioned pain modulation (CPM), once a pain signal is activated by a nociceptor stimulus from the periphery, this travels through the spinal cord to the subnucleus reticularis dorsalis modulating pain and sending the response by an efferent signal [179].

The rationale behind using tDCS relies on the capacity to potentiate the endogenous pain control system by anodal M1 stimulation activating the prefrontal cortex, the thalamus, the cingulate gyrus and the periaqueductal gray. These structures have a close communication to the subnucleus reticularis dorsalis, leading to a synergistic effect with the tDCS [28,39,182]. Some studies have described that motor cortex stimulation can enhance CPM in healthy [183–186]and chronic pain population [50,87]. For instance, Simis et al. 2015[187] and Reidler et al. 2012 [188] report a significant difference on pain threshold related to the combination of tDCS and CPM. Some other studies using tDCS have described a decrease in the use of opioid after surgery in conditions like total knee arthroplasty and lumbar spine surgery, supporting the enhancement of this endogenous pain system [91,92,189].

There are few studies on the use of tDCS before pain arises. Fregni et al. 2018[190]. in a factorial preclinical trial showed a significant increase of pain threshold with 8 sessions of tDCS applied before a chronic stress stimulus. Moreover, a clinical trial in 2017 reported a large effect size with 4 sessions of anodal M1 tDCS (2 sessions previous and 2 after hallux valgus surgery) leading to a lower postoperative pain compared to the sham tDCS group. In this study, the active tDCS group also decrease by 73% the use of analgesic after the surgery and significantly modulate the conditioned pain modulation system [21]. This effect could be related to the enhancement of the endogenous pain modulation system by thalamo-cortical pathway before the surgery.

Taken all together, current findings suggest that there is a need for more studies in order to support the use of tDCS for prevention of pain. Using tDCS as a preventive tool for pain might lead in the future to a decrease amount of opioids usage, morbidity and would improve the quality of life.

3.6. tDCS with extended number of sessions

It is known that tDCS can change spontaneous cortical excitability and as a consequence, contribute to the control of chronic pain [191]. Also, it is known that its effects involve changes in cortical plasticity; therefore, the repetition of the stimulus (in this case, tDCS) is critical. In fact,

although its beneficial effects on modulating pain are well established, there is heterogenous evidence regarding its efficacy clinical conditions due to the considerable variation of stimulation parameters applied in research study protocols. One very important parameter is the number of sessions. For some diseases, such as Fibromyalgia, short-term tDCS, ranging from 5 to 10 sessions, may not promote satisfactory outcomes on pain control[49,54,192], possibly due to an insufficient amount of electric current penetrating the brain along the treatment. To date, investigators believe that there may exist cumulative analgesic effects with repeated sessions[53] and, for this reason, extended treatments of tDCS, up to 60 sessions, are under investigation for particular groups of patients.

Mechanisms underlying the effects of tDCS on pain alleviation are not entirely comprehended. In patients with Fibromyalgia, it has been suggested that modifications in nociceptive pathways are crucial to prompt initiation and maintenance of pain [55]. There is a lack of inhibitory control over the somatosensory system in patients with chronic pain. Thus tDCS often promotes benefits by stimulating thalamic inhibitory networks [55,58]. Moreover, all tDCS parameters may influence stimulation effects on chronic pain. Focusing on treatment duration, investigators assume that short-term tDCS sessions may promote subclinical effects in refractory patients, while repetitive sessions for a longer period may have the capacity to stimulate neuroplastic changes further and consequently to modify the somatosensory processing [58,193].

A recent clinical trial of Brietzke et. al. (2019) on chronic pain patients has reported that an extended period of treatment with tDCS (60 sessions over 12 weeks) may induce large chronic pain decreases [23]– see above section on home-based tDCS. This finding agrees with a study with fibromyalgia patients which estimated that a prolonged treatment, with a minimum of 15 tDCS sessions, is ideal for reaching clinically meaningful outcomes on pain alleviation [55]. The analysed outcomes included not only the reduction of pain but also the quality of life. Another clinical trial assessed the dose-response of tDCS in a stepwise dose paradigm. In this phase II trial, investigators tested high definition tDCS over M1 with 2 mA of current delivery in patients with Fibromyalgia and its main goal was to determine the median number of sessions required to produce a 50% decrease level in perceived pain. A median time of 15 treatment days (3 weeks) was necessary to reach clinically meaningful outcomes [55].

Maintenance and boosting sessions of tDCS for chronic pain patients is not yet a common approach. As mentioned by Brighina et al. (2019) [194], more studies should be done with extended number of sessions to measure long lasting effects. Dawood Rahimi et al. (2020)[75] describes significant decrease of pain (frequency, duration, and intensity) after 22 sessions of stimulation over M1 and sensory cortex in migraine patients compare to the sham group. These sessions changed from three-times a week for five weeks to two-times a week for two weeks, and finally 1 stimulation for 3 more weeks. This describes a change in tDCS frequencies during a period of 10 weeks and measure the outcome after 12 months of follow up having a significant decrease of pain in migraine patients. Also, a fibromyalgia study has proposed to have 16 sessions of tDCS over motor cortex combined with exercise, 10 of these sessions would be done in consecutive days and six sessions as maintenance 3 times a week for 2 weeks [98]. This novel approach of maintenance and booster should be test in further studies.

Although the exploration of extended tDCS treatment is still incipient, it is considered a promising stimulation method for enhancing modulation of the somatosensory system and diminishing pain in refractory patients to the standard treatment.

4. Conclusions

TDCS has several advantages to become a useful clinical tool in the near future. In this article, we reviewed the current strategies of tDCS that have been tested and showed there is a good

amount of evidence supporting, for instance, motor cortex stimulation for the treatment of chronic pain. In addition, follow-up studies have tested protocols to increase its effect size, such as the combination of M1 tDCS with behavioural therapies (such as visual illusion and mirror therapy) and extended regimens of stimulation. Both strategies seem to result in larger effect sizes.

5. Expert opinion

5.1. Expert commentary

It has been shown that the stimulation of the prefrontal and primary motor cortex is efficient for pain reduction, however, a few other new strategies, such as high-intensity tDCS and network-based tDCS, are believed to induce strong neuroplastic effects, although the underlying neural mechanisms still need to be fully uncovered.

The field of neuromodulation in pain has been active to test alternative strategies, and we discussed here some new approaches such as selecting alternative targets (such as cerebellar tDCS) or using different electrical device parameters (such as tDCS using high-intensity currents and high-density tDCS - allowing up to 32 stimulating electrodes). It is still not clear whether these novel strategies will represent larger effect sizes, and the comparison between them and conventional montages and devices are needed, but especially a comparison with M1 tDCS will be critical in the future of the field.

Another vital area of research is to make tDCS more feasible for clinical use. The development of home-based devices is assumed to be determinant for the clinical translation of tDCS as it could reduce the high rate of dropouts since this overcomes the limitation of patients' travel to a specialized institution or hospital. We also discussed in this review the testing of home-based tDCS. Research on this strategy of stimulation has indeed advanced significantly in the past few years. These strategies discussed here will certainly lead to the design of pivotal studies to establish definite clinical evidence for tDCS in chronic pain.

Hence, conventional tDCS approaches demonstrated promising effects to manage pain, and new strategies are under development to enhance tDCS effects and make this approach more easily available for the patients in the clinical settings and in-home.

5.2. Five-year view

Future studies will examine the comparative effectiveness of conventional tDCS montages/targets and the novel strategies, particularly the comparison among conventional M1 tDCS – the tDCS montage with the highest level of evidence to reduce pain – and high-intensity/high-density tDCS approach on sensory-motor areas. This information will then be used to refine the already proved effective intervention and increase the efficacy of tDCS on pain.

In the next years, the mechanistic exploration of the neural pathways behind these effects will be a priority; these studies will lead to us to develop of easy-to-use biomarkers and response predictor to help to individualize the tDCS interventions in specific chronic pain populations.

Also, in the next years, the pivotal studies on home-based tDCS strategy will finally establish the efficacy and feasibility to translate the tDCS use to a more generalized use in the clinical area. Besides, the emerging novel strategies will be investigated using a home-based approach, such as home-based cerebellar tDCS, high intensity/density tDCS, home-based preventive pain protocols, and combination with behavioural interventions. This successful clinical translation will lead to explore the integration of tDCS interventions as a part of telemedicine programs and increase the availability of this effective and safe alternative therapy due to its lower potential of causing adverse effects when compared with standard pharmacological treatments.

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**** Evidence-based report on tDCS effects**

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*** Good example of a trial on tDCS and combination with behavioral intervention.**

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*** Important study on cerebelllar tDCS**

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Table 1. Summary of tDCS studies on pain management

Author	Study	Sample size	Anode	Cathode	Minute	Intensity	Area	Sessions	Combination	Results	Follow-up
M1 tDCS stimulation											
Fibromyalgia											
Mendonca et al. (2011)	RCT	30	Cervicothoracic	C3	20 min	2 mA	16 cm2	1	No	No significant pain decrease (VNS) after treatment	-
Mendonca et al. (2011)	RCT	30	C3	Cervicothoracic	20 min	2 mA	16 cm2	1	No	No significant pain decrease (VNS) after treatment	-
Villamar et al. (2013)	Crossover	18	C3	Cz, F3, T7, P3	20 min	2 mA	High-definition tDCS	1	No	Significant decrease of pain (VAS)	-
Fregni et al. (2006)	RCT	32	C3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of pain (VAS) after treatment and 21 days follow-up	3 weeks follow up
Roizenblatt et al. (2007)	RCT	32	C3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of pain (VAS) after treatment	-
Fagerlund et al. (2015)	RCT	48	C3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of pain (NRS) after day 4 of treatme	1 month follow up

										nt and after 30 days of follow up	
Valle et al. (2009)	RCT	41	C3	Contralateral SO	20 min	2 mA	35 cm2	10 (5 per week)	No	Significant decrease of pain (VAS) after treatment, 1 month and 2 month follow-up	1 and 2 months follow-up
Jales Junior et al. (2015)	RCT	20	C3	Contralateral SO	20 min	1 mA	15 cm2	10 (5 per week for 2 weeks)	No	Significant decrease of pain	-
Khedr et al. (2017)	RCT	40	C3	Contralateral arm	20 min	2 mA	24 cm2	10 (5 per week for 2 weeks)	No	significant decrease of pain (VAS) after treatment, 15 days and 1 month-follow up	15 days and 1 month follow up
Castilo-Saavedra et al. (2015)	Open label	14	C3	Cz, F3, T7, P3	20 min	2 mA	High-definition tDCS	Variable. At least 15 consecutive sessions	No	They estimate 15 tDCS sessions as the median number to reach clinically meaningful outcomes.	-
Riberto et al. (2011)	RCT	23	C3	Contralateral SO	20 min	2 mA	35 cm2	10 (once a week for 10 weeks)	Pain rehabilitation program	Significant decrease of pain (SF-Pain score). No significa	-

										nt VAS	
Mendonca et al. (2016)	RCT	45	C3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	Aerobic exercise	Significant decrease of pain (VNS) after treatment .	1 month and 2 month-follow up
Neuropathic Pain											
Ngernyam et al. (2013)	RCT	20	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	1	No	No significant decrease of pain (NRS)	-
Kikkert et al. (2019)	Crossover	17	C3/C4 (on the side oposite to amputation side)	Contralateral SO	20 min	1 mA	35 cm2	1	No	Significant decrease of phantom limb pain after 1 session and after 1 week of follow up	1 week-follow up
Attal et a. (2016)	RCT	35	C3/C4 on side opposite to maximal pain	Contralateral SO	30 min	2 mA	35 cm2	3 consecutive days	No	No significant difference (NPSI) after treatment and after 5 days of stimulation	5 days after last stimulation
Fregni et al. (2006)	RCT	17	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of pain (VAS) after treatment . No significant pain after 16 days follow-	16 days follow up

										up	
Wrigley et al. (2013)	Cross over	10	C3/C4 based on dominant hemisphere	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	No significant decrease of pain (NPS) after treatment, 4 weeks and 6 months-follow up	1 and 6 months-follow up
Thibaut et al. / Phase I (2017)	RCT	33	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of pain(VAS) at 4 week follow up	1 week and 3 month-follow up
Thibaut et al. / Phase 2 (2017)	RCT	9	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	10 (5 per week for 2 weeks)	No	Significant decrease of pain (VAS) at 1 week follow up	2 weeks, 1 and 2 months follow up
O'Neill et al. (2018)	Cross over	21	C3/C4 on side opposite to pain	Contralateral SO	20 min	1.4 mA	25 cm2	5 consecutive days	No	No significant decrease of pain (NRS) after treatment	-
O'Neill et al. (2018)	Cross over	21	Contralateral SO	C3/C4 on side opposite to pain	20 min	1.4 mA	25 cm2	5 consecutive days	No	No significant decrease of pain (NRS) after treatment	-

Auvichayapat et al. (2018)	Open label	10	C3	contralateral shoulder	20 min	2 mA	35 cm2	5 consecutive days	no	significant decrease of pain (NRS) in the end of treatment and 2 weeks follow-up and increases in both Glx/Cr and NAA/Cr in the ACC	2-weeks follow up
Lewis et al. (2018)	RCT	30	C3/C4 on side opposite to affected upper limb	Contralateral SO	20 min	1 mA	35 cm2	5 consecutive days	No	No significant decrease of pain (BPI) after treatment and follow up	56 days follow up
Bae et al. (2014)	RCT	14	C3/C4 opposite to hemiplegic side	Contralateral SO	20 min	2 mA	35 cm2	9 (3 per week for 3 weeks)	No	Significant decrease of pain (VAS) after 3 weeks of treatment	1-week and 3-week after
Boggio et al. (2009)	Crossover	8	C3/C4 on side opposite to maximal pain	Contralateral SO	30 min	2 mA	35 cm2	1	TENS (active/sham)	Significant decrease of pain (VAS) after TENS+tDCS and after only tDCS	-

Li et al. (2018)	Cros sover	12	C3 ip	Contrala teral SO	20 min	2 mA	35 cm2	1	Breathin g-controlle d electrical stimulatio n (BreESti m) to median nerve on dominant side	No significa nt decreas e of pain (VAS)	-
Soler et al. (2010)	RCT	39	C3/C4 on side opposite to maximal pain	Contrala teral SO	20 min	2 mA	35 cm2	10 (5 per week for 2 weeks)	Visual illusion/c ontrol illusion	Significa nt decreas e of pain (NRS) after treatme nt, 10 days and 3 months-follow up	10 days , 24 days and 3 mont h-follow up
Migraine											
Auvich ayapat et al. (2012)	RCT	37	C3	Contrala teral SO	20 min	1 mA	35 cm2	20 consecu tive days	No	Significa nt decreas e of pain (VAS) at the 1 and 2 month follow-up points.	1, 2, 3 mont hs follow up
Dasilva et al. (2012)	RCT	13	C3/C4 on side opposite to maximal pain	Contrala teral SO	20 min	2 mA	35 cm2	10 (every other day over 4 weeks)	No	No significa nt decreas e of pain after treatme nt (VAS). Significa nt decreas e of pain (VAS) after 4 months-follow up	2 and 4 mont hs follow up

Przeklasa-Muszynska et al. (2017)	RCT	50	C3/C4 on side opposite of dominant hemisphere	Contralateral SO	20 min	2 mA	35 cm2	10 (2 - 3 times per week for 4 weeks)	No	Significant decrease of pain (NRS) after treatment	-
Andrade et al. (2017)	RCT	13	C3	Contralateral SO	20 min	2 mA	25 cm2	12 (3 per week for 4 weeks)	No	Significant decrease of pain after treatment	-
Dawood Rahimi et al. (2020)	RCT	45	Left arm	C4	20 min	1 mA	cathode: 15 cm2, anode:35 cm2	22 sessions (3/week for 5 weeks and then 2 per week for 2 weeks and one/week in the last three weeks)	No	Significant decrease of pain frequency, duration and intensity in active cathodal M1 stimulation compare to sham	12 months follow up.
Grazzi et al. (2020)	RCT	135	C4	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	Stardarized drug withdrawal protocol	No significant difference between groups (anodal, cathodal, sham) in the percentage of reduction of days of headache and number of analgesics per month in patients with chronic migraine with	3, 6, 9 and 12 months after the enf of stimulation
Grazzi et al. (2020)	RCT	135	Contralateral SO	C4	20 min	2 mA	35 cm2	5 consecutive days	Stardarized drug withdrawal protocol		3, 6, 9 and 12 months after the enf of stimulation

										medication overuse. (12 month visit primary outcome)	
Low back pain											
Jiang et al. (2020)	RCT	60	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	Dry-electrode-based	1	No	Significant decrease of pain in active tDCS group	-
Straudi et al. (2018)	RCT	35	C3/C4 on side opposite to maximal pain, or dominant C3/C4 in case of central or bilateral pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	Group exercise	Significant decrease of pain (VAS) after 1 month-follow up.	1 month-follow up
Luedtke et al. (2015)	RCT	122	C3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	Cognitive behavioural management	No significant decrease of pain (BPI) .	24 weeks follow up
Jafarzadeh et al. (2019)	RCT	36	C3	Contralateral SO	20 min	2 mA	35 cm2	6 (3 per week for 2 weeks)	Postural training	Significant decrease of pain score (VAS) in the end of the treatment and one month after stimulation	1 month-follow up

Shiasy et al . (2020)	RCT	60	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	16 cm2	5 consecutive days	Attention bias modification (ABM)	Active tDCS+ABM group and ABM group showed significant descrease of attention bias and pain-related psychological outcomes compare to control and sham groups	1 month-follow up
Ostheoarthritis											
Ahn et al. (2018) / Suchting et al. (2020)	RCT	40	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of pain by NRS and increase of pain tolerance and pain threshold after active tDCS. Reduce levels of inflammatory cytokines IL-6, IL-10, and TNF-a and B-endorphin.	-

Ahn et al (2019)	RCT	40	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	higher circulating levels of β-endorphin at rest are associated with increased sensitivity to mechanical pain in older adults with knee OA.	-
Ahn et al. (2019)	Open label	20	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	10 consecutive days	No	Significant decrease of pain (VAS) after tDCS	-
Polloni ni et al. (2020)	Open label	10	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	10 consecutive days	No	Significant decrease of VAS and Osteoarthitis symptoms measure by WOMAC	-
Graca-Tarrago et al. (2019)	RCT	60	C3/C4 on side opposite to maximal pain	Contralateral SO	30 min	2 mA	35 cm2	5 consecutive days	Intramuscular electrical stimulus (EIMS)	Significant decrease of pain (VAS) with active tDCS and active EIMS	-
Ahn et al. (2019)	RCT	30	C3/C4 on side opposite to maximal	Contralateral SO	20 min	2 mA	35 cm2	10 consecutive days	mindfulness-based meditation	Significant decrease of pain (NRS) with	-

			pain							active tDCS and mindfulness-based meditation	
Myofascial pain											
Choi et al. (2014)	RCT	21	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	58	5 consecutive days	Trigger point injections	No significant decrease of pain (VAS)	-
Sakraja i et al. (2014)	RCT	31	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	Standard MPS therapy	Signigicant decrease of pain (VAS) after treatment an 1 week-follow up.	1 ,2, 3, 4 week follow up
Postoperative Pain											
Jiang et al. (2018)	RCT	22	C3	Contralateral SO	20 min	2	Dry-electrode-based	1	No	Significant decrease of pain (NRS) with active tDCS	-
Borckardt et al. (2013)	RCT	40	C1h or C2h based on target knee	F4	20 min	2 mA	16 cm2	4 (2/day x 2 postoperative days)	No	Significant difference in the use of patient-controlled analgesia pump. No significant difference in pain (VAS)	-

Khedr et al. (2017)	RCT	50	C1/C2 on side opposite to maximal knee pain	Ipsilateral arm	20 min	2 mA	25 cm2	4 consecutive days	No	Significant decrease of opioid consumption after treatment. Significant decrease of vas after treatment but not significant between groups.	-
Stamenkovic et al. (2020)	RCT	55	C3	Contralateral SO	20 MIN	1.2 MA	Current density 0.38 mA/cm2	5 consecutive days	No	Significant difference in the cumulative morphine dose in the first 120 h after surgery in the active tDCS group compare to sham. Significant difference in VAS pain in postoperative day 5 in the tDCS group compare to sham.	1 year
Preoperative tDCS											

Ribeiro et al. (2017)	RCT	40	C3	Contralateral SO	20 min	2 mA	35 cm2	2 consecutive days	No	Significant decrease of analgesic use, VAS cumulative worst daily pain and VAS during rest. No significant for VAS at worst pain and VAS when walking)	-
Other pain conditions											
Divandari et al. (2020)	RCT	16	C3 and F3	Contralateral SO	20 min	0.3 MA	Current density 0.1 mA/cm2	1	No	Significant decrease of pain for the active group compare to sham in cronic pelvic pain population	-
Thibaut et al. (2019)/ Phase I	RCT	31	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	10 (5 per week for 2 weeks)	No	No significant decrease of pain (BPI) after treatment and follow up .	2 weeks, 1 and 2 months follow up
Thibaut et al. (2019)/ Phase 2	RCT	21	C3/C4 on side opposite to maximal pain	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	No significant decrease of pain (BPI) after treatment and follow	2 weeks, 1 , 2 and 12 month follow up

										up .	
Ferreira et al. (2020)	RCT	20	C3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of bodily pain in both groups after 1 week, and only significant decrease pain after 2 weeks in the active tDCS group. Significant difference between groups for SF-36(primary outcome) in diabetic polyneuropathy	1 and 2 weeks after the last stimulation
DLPFC tDCS stimulation											
Fibromyalgia											
Fregni et al. (2006)	RCT	32	F3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	No significant decrease of pain (VAS)	-
Roizenblatt et al.(2007)	RCT	32	F3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	No significant decrease of pain (VAS)	-
Ting To et al. (2017)	RCT	42	F3	F4	20 min	1.5 mA	35 cm2	8 (2 per week for 4 weeks)	No	Significant decrease of pain (VAS)	-

										after treatment	
Valle et al. (2009)	RCT	41	F3	Contralateral SO	20 min	2 mA	35 cm2	10 (5 per week for 2 weeks)	No	Significant decrease of pain (VAS) after treatment	1 and 2 months follow-up
Brietzke et al. (2019)	RCT	20	F3	Contralateral SO	30 min	2 mA	35 cm2	60 (5 per week for 12 weeks)	No	Significant decrease of pain (VAS)	-
Silva et al. (2017)	RCT	40	F3	Contralateral SO	20 min	1 mA	35 cm2	1	Go/No-go Task		
Yoo et al.(2018)	RCT	58	F4	F3	20 min	2 mA	35 cm2	8 (2 per week for 4 weeks)	Occipital nerve stimulation	No significant decrease of pain (VAS).	-
Migraine											
Andrade et al. (2017)	RCT	13	F3	Contralateral SO	0.800, 20 min	2 mA	25 cm2	12 (3 per week for 4 weeks)	No	Significant decrease of pain scores (VAS) after treatment	-
Mansour et al. (2020)	RCT	18	F3	F4	20 min	2 mA	35 cm2	3 consecutive days	No	Prefrontral tDCS and occipital tDCS groups decrease significant the total number of migraine days in a week	1 week and 2 weeks

Dawood Rahimi et al. (2020)	RCT	45	Left arm	Between C4 and CP4	20 min	1 mA	cathode: 15 cm2, anode:35 cm2	22 sessions (3 per week for 5 weeks and then 2 per week for 2 weeks and one in the last three weeks)	No	Significant decrease of pain frequency, duration and intensity in active cathodal sensory cortex stimulation compare to sham	12 months follow up.
Myofascial pain											
Choi et al. (2014)	RCT	21	F3	Contralateral SO	0.571, 20 min	2 mA	58 cm2	5 consecutive days	Trigger point injections	Significant decrease of pain scores (VAS) after treatment	-
Orofacial pain											
Fricova et al. (2019)	RCT	15	F3/F4	F3/F4	20 min	1 mA	.	5 consecutive days	No	Decrease of pain (VAS) after treatment	2 weeks-follow up
Postoperative pain											
Dubois et al. (2013)	RCT	59	F3	Above right ear	0.286, 20 min	1 mA	35 cm2	1 (postoperative)	No	No significant diference of pain (VAS) or opioid consumption	-
Dubois et al. (2013)	RCT	59	Above right ear	F3	0.286, 20 min	1 mA	35 cm2	1 (postoperative)	No	No significant diference of pain (VAS) or opioid consumption	-

Borckardt et al. (2013)	RCT	58	C1h or C2h based on target knee	F4	1.250, 20 min	2 mA	16 cm2	4 (2/day x 2 postoperative days)	No	Significant difference in the use of patient-controlled analgesia pump. No significant difference in pain (VAS)	-
Glaser et al. (2016)	RCT	27	Cz	F4	20 min	2 mA	.	4 (2/day x 2 postoperative days)	No	Significant lower use of opioids and pain (NRS) at its least. No significant decrease of pain (NRS) average or pain at its worst	-
Other pain conditions											
Divandari et al. (2020)	RCT	16	C3 and F3	Contralateral SO	20 min	0.3 MA	Current density 0.1 mA/cm2	1	No	Significant decrease of pain for the active group compare to sham in chronic pelvic pain population	-
Ramalho et al. (2020)	RCT	26	F3	Contralateral SO	20 min	2 mA	35 cm2	5 consecutive days	No	No significant difference of pain between groups	
Cerebellar tDCS stimulation											

Phantom limb pain											
Bocci et al. (2019)	Cros sover	14	Median line, 2 cm below the inion, with lateral borders about 1 cm medially to the mastoid apophysis,	Right shoulder	20 min	2 mA	35 cm2	5 consecutive days	No	Significant decrease of paroxysmal pain after treament and 4 weeks-follow up. No significant improvement of phantom limb pain (VAS) after treatment.	2 weeks and 4 weeks-follow up
Spinal tDCS stimulation											
Neuropathic Pain											
Choi et al. (2019)	Cros sover	10	Thoracic spinal cord (over the spinous process of the tenth thoracic vertebra)	Cz	20 min	2 mA	35 cm2	1	No	No significant difference decrease of pain between groups	-
Berra et al. (2019)	RCT	33	Thoracic spinal cord (over the spinal process of the tenth thoracic vertebra)	Right shoulder	20 min	2 mA	35 cm2	10 consecutive days	No	Significant decrease of pain (neuropathic pain symptoms inventory) after 10 days of stimulation and follow-up	1 month-follow up