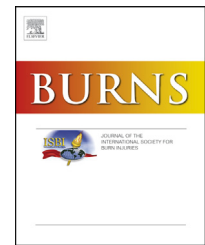


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Review

A review of burn symptoms and potential novel neural targets for non-invasive brain stimulation for treatment of burn sequelae

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ABSTRACT

Burn survivors experience myriad associated symptoms such as pain, pruritus, fatigue, impaired motor strength, post-traumatic stress, depression, anxiety, and sleep disturbance. Many of these symptoms are common and remain chronic, despite current standard of care. One potential novel intervention to target these post burn symptoms is transcranial direct current stimulation (tDCS). tDCS is a non-invasive brain stimulation (NIBS) technique that modulates neural excitability of a specific target or neural network. The aim of this work is to review the neural circuits of the aforementioned clinical sequelae associated with burn injuries and to provide a scientific rationale for specific NIBS targets that can potentially treat these conditions. We ran a systematic review, following the PRISMA statement, of tDCS effects on burn symptoms. Only three studies matched our criteria. One was a feasibility study assessing cortical plasticity in chronic neuropathic pain following burn injury, one looked at the effects of tDCS to reduce pain anxiety during burn wound care, and one assessed the effects of tDCS to manage pain and pruritus in burn survivors. Current literature on NIBS in burn remains limited, only a few trials have been conducted. Based on our review and results in other populations suffering from similar symptoms as patients with burn injuries, three main areas were selected: the prefrontal region, the parietal area and the motor cortex. Based on the importance of the prefrontal cortex in the emotional component of pain and its implication in various psychosocial symptoms, targeting this region may represent the most promising target. Our review of the neural circuitry involved in post burn symptoms and suggested targeted areas for stimulation provide a spring board for future study initiatives.

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Abbreviations: M1, primary motor cortex; NIBS, non-invasive brain stimulation; PTSD, post-traumatic stress disorder; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation.

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Contents

1. Introduction	00
2. Search methodology	00
3. Results	00
3.1. Burn symptom 1: pain	00
3.2. Burn symptom 2: pruritus	00
3.3. Burn symptom 3: psychosocial disorders	00
3.4. Burn symptom 4: sleep disturbance	00
3.5. Burn symptom 5: fatigue	00
3.6. Burn symptom 6: impaired motor strength	00
4. Discussion	00
5. Conclusion	00
Funding	00
Conflict of interest	00
Acknowledgments	00
References	00

1. Introduction

Burn survivors experience myriad associated symptoms such as pain, pruritus, fatigue, impaired motor strength, post-traumatic stress, depression, anxiety, and sleep disturbance [1]. Many of these symptoms are common and remain chronic, despite current standard of care. Given these persistent symptoms, there is a need for novel targeted interventions. Burn injuries often have lasting ramifications on survivor physical and mental health. In regards to mental health, symptoms of post-traumatic stress, depression, and anxiety have been observed persisting after injury, creating lasting psychosocial consequences with impact on social functioning and disability [2]. About a third of burn survivors report moderate to severe psychological or social difficulties [3,4] which dramatically impact return to work, social integration, and consequently quality of life [5]. Similarly, symptoms of pain and pruritus cause equally concerning sequelae for burn patients, affecting sleep [6], daily activities [7], and quality of life [8]. The prevalence and chronicity of these post burn symptoms therefore underscores the need to identify effective therapies to ameliorate these symptoms and ensuing effects. Treatment of these chronic symptoms would thus have an impact on many patients' quality of life.

One potential novel intervention to target these post burn symptoms is low intensity transcranial electrical stimulation (tES) [9]. tES is a non-invasive brain stimulation (NIBS) technique that modulates neural excitability of a specific target or neural network. Most studies used transcranial direct current stimulation (tDCS), which modulates cortical excitability through the application of a weak electrical current in the form of direct current brain polarization [10]. Another technique is transcranial alternating current stimulation (tACS), which is similar to tDCS but it oscillates a sinusoidal current at a specific frequency to interact with the brain's natural cortical oscillations [11]. In the current literature, tES has been shown to reduce pain, improve motor function, enhance cognitive abilities and treat depression in various

populations. However, there is a paucity of literature in regards to tES use on post-burn sequelae.

The aim of this work is to review the neural circuits of the aforementioned clinical sequelae associated with burn injuries and to provide a scientific rationale for specific non-invasive brain stimulation targets that potentially treat these conditions. This review focuses on the adult population only as the issues associated with growth and development of the brain in the pediatric population are extremely complex. We review the mechanisms in which tES modulates these neural circuits and their related behaviors in various patient populations as well as the current state of the science on tDCS to improve burn related symptoms. Given that the current literature is limited in the burn population, this review aims to provide a model-driven approach for potential neural targets to treat burn associated symptoms that will open areas of future inquiry in the field of burn care.

2. Search methodology

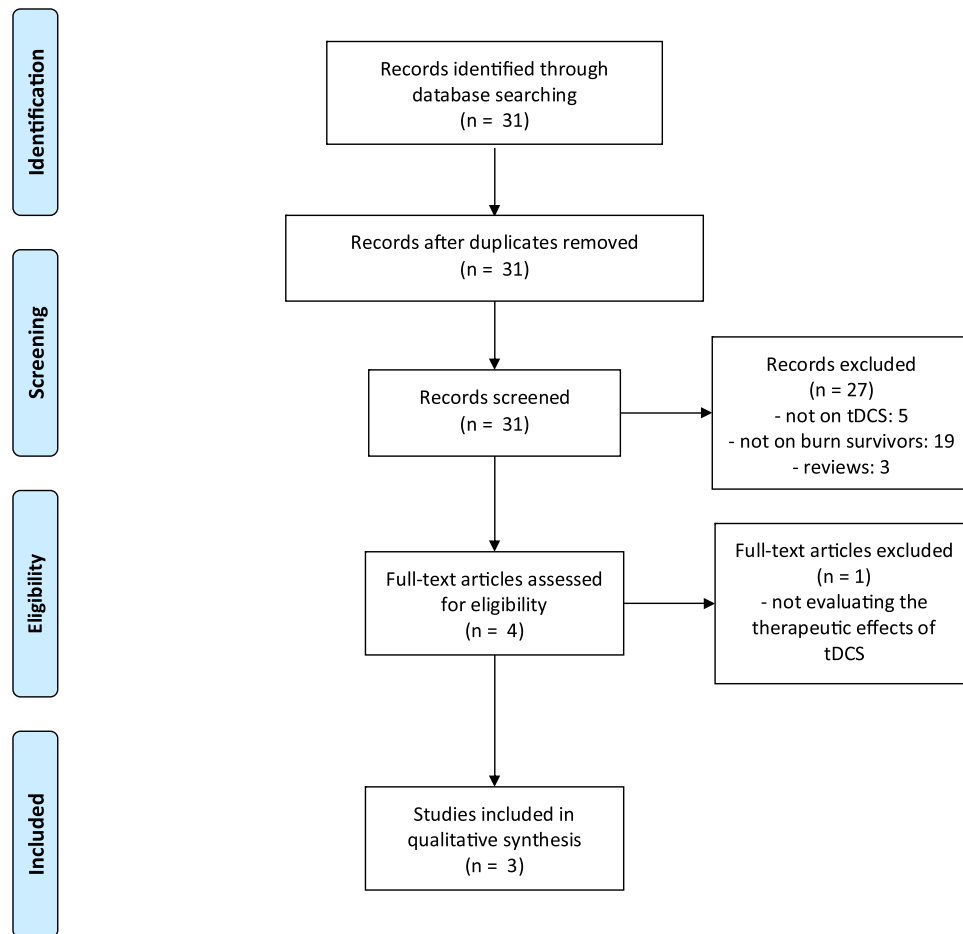
We searched on PubMed using the following search terms: "burn" and tDCS "transcranial direct current stimulation" or "neuromodulation" or "non-invasive brain stimulation".

We included studies investigating the effects of tDCS on burn related symptoms (i.e., pain, pruritus, psychosocial disorders, sleep disturbance, fatigue and impaired motor strength) in burn survivors. We included case-reports, open-label studies and randomized clinical trials. We excluded studies not written in English or French, reviews or opinion papers, conference abstracts, and those not using tES to treat burn related symptoms in burn survivors.

We followed the PRISMA statement to evaluate the articles we found and reported the results.

3. Results

31 studies were found; only three matched our inclusion criteria (see flowchart) [12–14].



Two studies have investigated the effects of tDCS on pain when applied over the motor cortex (M1). A first pilot study including 4 patients with burn injury and chronic pruritus showed that a single session of active anodal tDCS over the primary motor cortex induced a decrease in cortical excitability (i.e., decreased alpha activity in the occipital area and low beta activity in the frontal area) [12]. Another study using similar parameters (anodal tDCS over M1) evaluated the effects of 10 sessions of tDCS on pain and itch levels in 31 burn survivors [14] but active tDCS did not influence pain or itch levels. Finally, one randomized control trial on 60 patients tested the effects of a single session of cathodal (or sham) tDCS over the sensory cortex aiming to reduce self-reported pain and anxiety [13]. Pain and anxiety scores were significantly lower in the active tDCS group compared with the sham group.

3.1. Burn symptom 1: pain

Pain management after burn injury is critical since it may have an important impact on burn recovery and quality of life [15,16]. Almost half of burn survivors still present with pain years after the incident [17]. Further, two-thirds of survivors report that pain interferes with their rehabilitation, and about half report that pain interferes with their daily lives [17], thus underscoring the significant impact of pain on patients' quality of life. Pain is therefore a critical element to consider at the acute, rehabilitative, and chronic phases of burn

recovery. In the acute stage, following burn injury, some nerve endings are undamaged, resulting in the experience of significant pain at the site of the injury. Conversely, if the nerve ending is entirely destroyed, excised or significantly damaged, the injured area is insensate, and does not experience pain. Burn survivors may also suffer from neuropathic-like pain, which can become chronic [18]. Chronic pain conditions are characterized by several maladaptive neural changes, such as central sensitization [19].

Acute pain perception begins with activation of peripheral nociceptors and via the spinothalamic tract that reaches the thalamus and the somatosensory cortex. In acute pain, processes are in place to prevent tissue damage. However, this pain may become chronic when maladaptive neural changes occur, including central sensitization [20]. The neural mechanisms of central sensitization in chronic neuropathic conditions are only partially understood [21,22]. Both acute and chronic pain processes are multidimensional, comprising of nociceptive, cognitive, emotional, and affective components, each of these relating to specific brain structures [23]. Cortical and subcortical brain areas have been investigated in previous studies and associated with a common formation called the *pain matrix* [23,24]. This large neural network consists of the primary and secondary somatosensory cortex, the prefrontal lobe, anterior cingulate cortex, amygdala, insula, and the thalamus. Besides the somatosensory areas activated during pain, neuroimaging studies have also

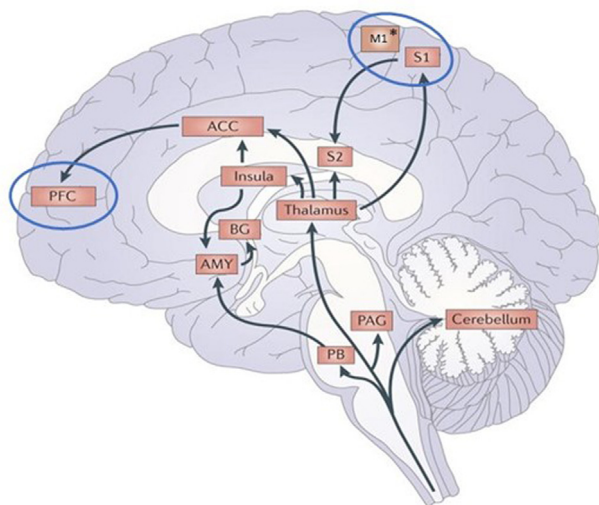


Fig. 1 – Afferent pain pathways. Nociception information from the spinal cord reach the thalamus, parabrachial nucleus (PB), and the periaqueductal grey nucleus (PAG). From the thalamus, nociception information is projected to the insula, anterior cingulate cortex (ACC), primary somatosensory cortex (S1), and secondary somatosensory cortex (S2). From the ACC, the prefrontal cortex (PFC) will also be activated. Whereas from the PB, information will reach the amygdala (AMY) and is then projected to the basal ganglia (BG). Cortical targets to modulate pain perception via non-invasive brain stimulation are enclosed within the blue circles. M1 represent the primary motor cortex, preferably selected as a target. *the stimulated region overlaps M1 and S1. Adapted from [27].

demonstrated that the dorsolateral prefrontal cortex, thalamus and medial prefrontal cortex play a crucial role in pain modulation as well [25,26]. In addition, the anterior cingulate cortex and the insula, part of the limbic system, are also important for the emotional aspects of pain [27] (Fig. 1).

tDCS applied over the sensorimotor cortex may help in normalizing pain processes and managing neuropathic pain symptoms. Many studies have demonstrated the analgesic effects of tDCS applied over the somatosensory cortex, as well as over the prefrontal cortex to reduce pain level in various conditions, such as fibromyalgia, osteoarthritis or chronic visceral pain (for a review see [28]). In healthy subjects, tDCS has been shown to modulate the pain threshold and conditioned pain modulation [29], a marker of the endogenous pain inhibitory system, which is altered in patients with neuropathic pain [30]. Given that burn injury may result in the development of chronic neuropathic pain due to central neural changes associated with sensory deafferentation, tDCS applied over the sensorimotor cortex may induce a decrease in maladaptive plasticity and therefore reduce pain in patients with burn injuries. The rationale for motor cortex stimulation is to enhance thalamocortical connectivity and thus compensate for some of the lost sensory afference that is observed with severe burn injury [31]. In fact, the goal is to enhance activity of primary motor cortex with anodal tDCS.

In the current literature of burn injury only two studies have investigated the effects of tDCS on pain when applied over the motor cortex (M1). A first pilot study including 4 patients with burn injury and chronic pruritus showed that a single session of active anodal tDCS over the primary motor cortex induced a decrease in cortical excitability (i.e., decreased alpha activity in the occipital area and low beta activity in the frontal area) [12]. Another study using similar parameters (anodal tDCS over M1) evaluated the effects of 10 sessions of tDCS on pain and itch levels in 31 patients [14]. However, in this study, active tDCS failed to reduce pain or itch intensities at the end of the 10 sessions and at follow-up. The main reason is likely because the subjects in such study had more pruritus than pain [14].

A third study tested the effect of tDCS on pain and anxiety during burn wound care in acute patients [13]. The authors found that a single cathodal tDCS session applied over the sensory cortex induced a significant reduction of about 10% of anxiety related to pain, compared to the sham group.

Given the limited literature on this topic, further studies are merited to investigate the potential therapeutic benefits of this modality on post-burn pain. We also suggest that such studies should include subjects with truly neuropathic pain as the main component of pain.

3.2. Burn symptom 2: pruritus

Pruritus is a commonly reported symptom among burn survivors affecting as many as 87% of survivors 3 months post-injury and still 67% at 24 months post-injury [32]. Factors found to be predictors of itch include deep dermal injury, post-traumatic stress symptoms, female gender, total burn surface area >40%, and injuries requiring >3 weeks to heal [32]. Further, post-burn pruritus has been demonstrated to significantly impact survivor quality of life, affecting sleep, activities of daily living, and psychosocial health [6]. As many as 94% of survivors with chronic pruritus in a cross-sectional study described it as unbearable and as many as 86% of survivors with acute itch described it as unbearable as well [6].

The primary mechanism of itch involves mediation of the A-delta and C-nociceptors [33] in the top layers of the skin [34] with activation of the primary somatosensory cortex, located in the post-central sulcus and the secondary somatosensory cortex, located in the upper lateral sulcus [35]. Once a pruritogenic agent instigates the itch mechanism, unmyelinated C fibers activate and relay the sensation of itch to the brain [33,36]. In addition, it is hypothesized that peripheral sensitization decreases the activation threshold and thus increases the activity of itch-related receptors and nerve fibers [36]. Central sensitization, however, occurs in the spinal cord and brain, and causes non-pruritic stimuli to be presented instead as itch, thus increasing and exacerbating the symptomology of itch [36]. Neuropathic itch, however, may result from increased peripheral firing or impaired central inhibition of neurons involved in the itch neural pathway [37] which may be related to a compensatory mechanism. Patients with chronic itch have been noted with developed changes in the excitability and organization in their brains [34].

Despite the frequency of reported pruritus among survivors, the modulation of this symptom with tDCS is not well investigated in literature thus far. It is hypothesized that tDCS

can reduce symptoms of pruritus by modulating pathways of neuronal firing and affecting neural excitability [38,39]. The neural pathway of itch has been noted to be closely associated with that of pain, specifically with overlap in pain-processing networks [34]. Correspondingly, tDCS modulates pain processing pathways including the periaqueductal gray area, with evidence of itch relief [34,35]. However, differences in the two pathways remain. While closely related, chronic pain seemingly involves more extensive changes in neuroplasticity compared to chronic itch, thus resulting in decreased receptiveness to tDCS stimulation compared to itch [34]. In addition, brain areas involved in pruritus involve activation of the thalamus, somatosensory cortex, parietal cortex, motor areas (primary, supplementary, premotor cortex). However, in differentiation to pain, the secondary somatosensory cortex is not activated with itch symptoms [40].

In a study on healthy subjects and histamine induced itch sensation, bi-hemispheric tDCS has been more effective than uni-hemispheric tDCS for symptom alleviation [41]. In a case report by Knotkova et al. (2013), a patient with chronic pruritus was administered 20 minutes of tDCS for 5 days with resultant reduction in pruritus for 3 months [34].

In the setting of burn injury related itch, a study noted that active tDCS over M1 was ineffective in treating itch reported by burn injury patients while the sham condition tDCS effectively decreased symptoms two weeks after stimulation [14]. tDCS increases the sensory threshold, as shown in healthy subjects [29] and may thus decrease the response to peripheral sensory afference of itch, leading to such effects [14]. In fact, we hypothesized in that study that tDCS for chronic pain would be different than tDCS for chronic pruritus. In the latter case, an inhibitory tDCS may be effective. Currently, no other studies have investigated the use of tDCS in alleviating post burn pruritus, or in other populations of patients. Therefore, given the lack of literature in regards to burn related itch and tDCS, further investigation is merited on the topic.

3.3. Burn symptom 3: psychosocial disorders

Psychosocial disorders encompass, among others, anxiety, depression and post-traumatic stress disorder (PTSD). Anxiety refers to feelings of excessive fear, worry, and unease caused by external or internal potential threats [42] lasting greater than 6 months [43]. Depression is characterized by low mood often in concordance with low self-esteem, loss of interest in normally enjoyable activities, and low energy for at least two weeks [44]. Finally, PTSD is defined as a mental disorder caused or triggered by exposure to either death, serious injury, or sexual violence [43]. Symptoms may include disturbing thoughts, feelings, or dreams related to the events, mental or physical distress to trauma-related cues, and attempts to avoid trauma-related cues [45].

Following a burn injury, rates of depression are high, reported up to 10–23% at 1 year post-injury [46]. Some factors, such as severity of pain, have been shown to be a predictor of suicidal ideation [47]. Therefore, pain management may help manage depression and reduction of suicidal ideation. Similarly, the prevalence of PTSD in burn survivors can be as high as 40% at 6 months and up to 45% at 12 months post-injury [2]. Main symptoms reported by survivors include sleep

disturbances, recollections of the injury and avoidance of thoughts or feelings associated with the burn and distress when reminded of the burn.

Studies have reported high rates of PTSD in burn survivors ranging from 20% to 69% [48–50]. Main symptoms comprise of sleep disturbances, recollections of the injury and avoidance of thoughts or feelings associated with the burn and distress when reminded of the burn [51]. The high incidence and severity of PTSD have been associated with extensive post-burn scarring, female gender, large burn surface area, pre-traumatic depressive behaviors, low psychological resilience, and inadequate social support [49].

The prefrontal area, similar as for other psychosocial dysregulation pathologies, plays a critical role. Indeed, the neural correlates of these psychiatric disorders, neuroimaging and lesion studies have identified the medial prefrontal cortex (mPFC) as one of the main structures involved [52–54]. More specifically, PTSD is thought to be linked to a dysregulated neurocircuit that mainly involves the amygdala, prefrontal regions, and hippocampus. A recent meta-analysis of transcranial magnetic stimulation (TMS) on the mPFC in psychiatric disorders confirms the involvement of this key structure in the management of such symptoms [55].

tDCS use in management of depressive symptoms has been widely studied. Regarding the most efficient target, tDCS studies focusing on the prefrontal region have shown to reduce depression symptoms in multiple studies [56]. The most well-known trial is the ELECT non-inferiority trial published in 2017 [57] in which the anode and cathode were placed on the left and right dorsolateral prefrontal cortexes of participants for a total of 22 sessions. This study demonstrated the non-inferiority of tDCS as compared to escitalopram and that both escitalopram and tDCS were superior to placebo in reducing depression [57].

From a therapeutic perspective, it is hypothesized that tDCS treatment over the prefrontal areas may help management of executive control of fear responses and thus, reduce PTSD symptoms. In this context, tDCS applied over the prefrontal area has been investigated for various psychiatric disorders including reduction of PTSD symptoms with promising results in veterans with PTSD [58,59]. Besides PTSD, tDCS has also been demonstrated to reduce stress levels when applied over the prefrontal region (i.e., right medial-prefrontal cortex [60]). An increase in cerebral blood flow was observed in the right medial-prefrontal cortex and in the amygdala after 20 minutes of anodal tDCS. These results demonstrated that application of tDCS over the prefrontal cortex may reduce stress and PTSD symptoms in patients with burn injuries.

For depression and PTSD not related to a burn injury (e.g., in veterans), the prefrontal area may be the best region to target for treatment. No clinical trial, or open-label studies have tested the effects of prefrontal tDCS on these symptoms in patients with burn injuries. Following a protocol looking at the effect of M1-tDCS on pain and itch level, the injury's psychosocial impact was also measured (see supplementary material). The data demonstrates that tDCS, when applied over M1 did not induce a significant improvement on impact of event, depression, anxiety, or sleep. It may be hypothesized that, if pain and/or itch levels would have been reduced following M1-tDCS [14], an impact on the associated

psychiatric symptoms may have been observed via an indirect pathway. However, as neither improvement of pain nor itch was observed in this study, it may explain why no reduction of depression, PTSD or anxiety was found and targeting the prefrontal area may induce stronger effects as for other populations.

Indeed, tDCS applied over the prefrontal region has been shown to reduce depression [61] and PTSD symptoms [62] in patients suffering from these pathologies.

3.4. Burn symptom 4: sleep disturbance

Sleep disturbances encompass disorders of initiating and maintaining sleep, excessive somnolence, sleep–wake schedule perturbation, and any dysfunctions associated with sleep, sleep stages, or partial arousals [63]. Sleep disturbance can be due to traumatic experience, psychiatric disorders or neurological diseases. Though sleep affects a significant proportion of the population, little is known about the exact mechanisms of these symptoms given the heterogeneous nature of the disorders [64].

Among the burn survivor population, sleep disturbance may be related to pain, itch or behavioral health conditions. The proportion of patients with sleep disturbance following a burn injury is as high as 74%. Most frequently reported problems include nighttime awakenings, daytime napping, nighttime pain and difficulty with sleep onset [65]. Poor sleep quality has been shown to be associated with high levels of pain and analgesic intake during the day and a myriad of other symptoms [66].

Some recent studies have shown the positive effects of tDCS on sleep to promote vigilance and sleepiness [67]. Specifically, prefrontal tDCS applied during a wake period may improve the quality of subsequent sleep [68,69] in two different conditions, post-polio syndrome [68] and euthymic bipolarism [69]. tDCS may also improve sleep efficiency in patients with fibromyalgia [70]. Another study tested the effects of prefrontal stimulation applied during stage 2 sleep. In this study, tACS (transcranial alternating current stimulation) at 0.75 Hz in insomniac patients was used. Prefrontal tACS may thus ameliorate sleep quality and decrease the number of wake times after sleep onset [71]. These behavioral findings were coupled with electrophysiological changes as an increase of stage 3 duration and a decrease of stage 1 duration were also observed.

Based on the current literature on non-invasive brain stimulation to manage sleep disturbance, the prefrontal area has been shown to be an effective target both when stimulated during wakefulness and during sleep. Unfortunately, there are no current studies in burn outcomes evaluating the effects of tDCS on sleep quality. As mentioned previously, M1-tDCS applied in patients with burn injuries did not lead to sleep quality improvement. As sleep disturbance is linked to pain and itch, it may also explain why M1-tDCS did not promote sleep. Therefore, targeting the prefrontal region may induce more promising effects.

3.5. Burn symptom 5: fatigue

Fatigue is a common symptom reported after burn injury, with many patient reports of persistence even at 24 months post-

injury [72]. Symptoms of fatigue may contribute negatively to a survivor's recovery from hindering their ability to fully participate in rehabilitation exercises to affecting injury healing [73]. Larger burn size was found to be associated with symptoms of fatigue [72]. Further, post-injury fatigue has been demonstrated to impact survivors' post-injury quality of life as well as work-related disability [74]. Given the persistent implications of fatigue on quality of life, it is therefore imperative that future research targets strategies to alleviate this post-burn sequela.

Fatigue is oftentimes subjective and is defined clinically by an increased sense of effort in the initiation and maintenance of both physical and cognitive activities [75]. Fatigue may be further categorized as myopathic or subjective fatigue. Symptoms of myopathic fatigue are due to muscle weakness resulting from decreased muscle force output [75]. This type of fatigue is common among patients with myopathic disorders, neuromuscular junction disorders, and peripheral nerve disorders. Conversely, symptoms of subjective, or cognitive, fatigue are due to lesions in pathways implicated in arousal and attention, the basal ganglia, and the reticular and limbic systems [75]. This type of fatigue is more commonly noted in peripheral, autonomic, and central nervous system disorders [75].

Cognitive fatigue, differing from myopathic fatigue, is observed in most acute and chronic inflammatory diseases [76]. In chronic inflammatory disorders, fatigue has been found to be correlated with high observed levels of inflammatory cytokines such as IL-6, IL-1, and TNF [77]. It is hypothesized that the increased levels of these markers signal the central nervous system to subsequently respond and generate the feeling of fatigue. Similarly, in burn injury, inflammation markers of IL-6, TNF- α , and IL-1 β are also released, contributing to the stress response and thus likely to the symptoms of fatigue as well [78].

tDCS has been previously investigated for treatment of fatigue, specifically, in multiple sclerosis (MS). In the treatment of multiple sclerosis, tDCS modulates the postulated disrupted cortico-subcortical loop [79]. In addition, in the disease process of multiple sclerosis, neural cell axons become demyelinated due to a combination of inflammation, demyelination, and oxidative stress [80]. tDCS is also thought to improve the activation and migration of neural stem cells and therefore promote axonal regeneration [79,81]. By improving conduction through axonal regeneration of the demyelinated neural cell axons [80], tDCS may further alleviate symptoms of fatigue [79,80]. Given the implications of inflammation and fatigue, tDCS may work to modulate this post burn fatigue through similar mechanisms as with fatigue observed in MS. Further, while no studies have investigated the use of tDCS on post-burn fatigue, previous studies have noted the use of tDCS in subjective cognitive fatigue. tDCS has been demonstrated to have a positive effect on patients with mild-moderate cognitive fatigue compared to patients with severe cognitive fatigue with parietal stimulation [82]. In addition, tDCS stimulation, applied over the parietal and frontal area, was able to improve fatigue-related reaction time while performing cognitive tasks [82,83].

Currently, there has not been literature demonstrating the use of tDCS in treating symptoms of fatigue after burn injury.

However, given the efficacy of tDCS in improving multiple sclerosis related fatigue, tDCS applied in the parietal and frontal area may be a likely target for future investigation with promising results. Given the safety profile and ease of implementation, tDCS may be a potential favorable treatment option to alleviate fatigue [38,84], especially given pharmacologic limitations in treatment that patients may encounter [79].

3.6. Burn symptom 6: impaired motor strength

Muscular weakness is commonly reported after burn injury whether due to muscle wasting or due to the increased catabolism of skeletal muscle, with resultant loss of body mass, experienced after injury [85,86]. Critical illness polyneuropathy, a diffuse neuropathy that may occur with severe burn injuries, may be another source of weakness, causing extremity flaccid weakness due to axonal damage of the motor neurons [87]. The degeneration of sensory and motor neuron nerves leads to resultant skeletal muscle degeneration [88] and subsequent symptoms of motor weakness. Among the burn population, this type of weakness occurs anywhere between 2% and 29% of survivors [89,90]. Predictors of impaired motor strength, or muscular weakness, include initial myostatin serum concentration levels and greater total burn surface area [91]. In order to generate fine distal movements, activation of the primary motor cortex is required [92]. When one side of the motor cortex becomes impaired, increased transcallosal inhibition from the unaffected motor cortex to the affected cortex disrupts the primary motor cortex. The resultant decrease in cortical excitability thereby impairs muscle strength [92–94].

tDCS has been shown to be efficacious in improving motor function and strength in variable disorders through activation of motor areas and enhancement of action potentials for movement execution when applied over M1 [95]. Anodal tDCS increases motor learning by decreasing GABAergic activity in the motor cortex and subsequently increasing functional connectivity of the motor network [96]. Various studies have demonstrated positive effects of tDCS stimulation on movement and strength improvement. In a study by Kim et al, anodal tDCS applied to the affected hemisphere of patients with subacute stroke was found to improve function of the affected hand [97]. Similarly, in a study of children with spastic hemiparetic cerebral palsy, anodal M1 tDCS was noted to improve upper limb movements of these patients as quantified through decreased total movement duration time, decreased returning movement time, and overall reduced movement execution time [95]. Further, M1 tDCS may also improve the maximum force of knee extension in patients with chronic subcortical stroke [98], an effect suggested to be resultant of tDCS induced corticospinal excitability over the lower limb primary motor cortex [39,99,100]. Finally, several studies have shown that motor cortex stimulation does enhance exercise performance, including muscle strength and also physical endurance [101–104].

Though other therapies such as strength training [86] have been demonstrated to be efficacious improving muscular strength post burn injury, the role of tDCS in affecting this symptom has not been investigated. However, given the

positive outcomes of tDCS applied over the motor cortex observed in other disorders, future studies may be focused on this area of stimulation.

4. Discussion

There is evidence in other fields that suggest that tES may be a successful treatment for common post burn symptomology. Although there is a lack of data on the effects of tES in the burn population, given the frequency of chronic symptoms there is a need for novel interventions. This paper reviews prior literature to develop an anatomical map of potential areas of brain stimulation to treat burn symptoms. Many burn symptoms share well described neurophysiology seen in other populations and literature examining the utility of tES treatments.

Based on these observations we can draw three main conclusions: (1) The prefrontal cortex may be a better target than the motor area to reduce both pain and psychosocial symptoms related symptoms. (2) tES applied over the parietal cortex may help with fatigue and improve vigilance, though data is limited even in other conditions. (3) tES applied over M1 could be useful to help with muscle weakness in the subpopulation of patients with burn suffering from motor disorders.

1. tES applied over the prefrontal area has been shown to improve cognitive symptoms, such as attention and memory, in various pathologies [e.g., 105,106], as well as to help with psychosocial symptoms of PTSD or anxiety and sleep disturbance [e.g., 107,108]. In addition, the prefrontal region may also play a role in the emotional reaction to pain. In the past decade, many neuroimaging and neurophysiological studies have demonstrated the critical role of the DLPFC not only in pain processes [109] but also in fatigue [79], depression [110], or attention [111], including the attentional circuit dedicated to noxious stimuli [112]. Therefore, modulating the prefrontal cortex via non-invasive brain stimulation could also help manage acute and neuropathic pain in patients with burn injury. Similar to management of fibromyalgia or neuropathic pain in patients with multiple sclerosis [113], tES over the prefrontal area did show promising analgesic effects. Similar montage should also be tested in patients with burn injury. This approach appears more promising as this population of patients often suffers from depression and fatigue, symptoms involved by the prefrontal area.
2. tES applied over the parietal cortex may be efficacious in reducing fatigue, as previously investigated, such as in multiple sclerosis. In addition, the parietal cortex is also involved in itch regulation as demonstrated by neuroimaging studies. tES effects on fatigue may be linked to an improvement of vigilance level, as neuroanatomically, vigilance depends on a network involving the brainstem, the thalamus, and the frontal and parietal cortices [114].
3. tES applied over the motor cortex may still be useful to help rehabilitation, especially when patients remain bedridden for an extended period of time and suffer from ensuing muscle weakness. Patients with extensive burn injuries

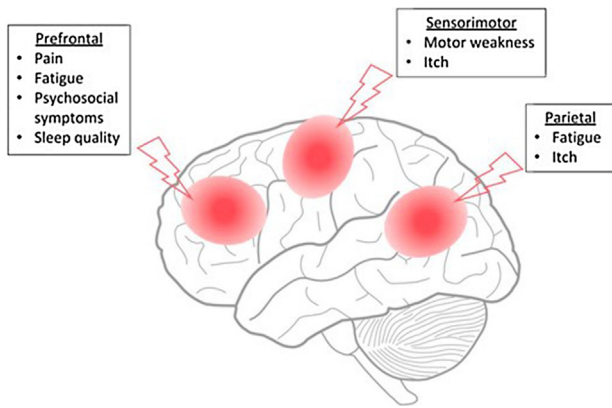


Fig. 2 – Main suggested cortical regions (red circles) for target treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

often stay in intensive care units before beginning rehabilitation therapy. During this time, muscle atrophy can occur, consequently slowing down functional improvement. In this scenario, applying tES over the motor cortex during rehabilitation may speed up the functional recovery. However, based on our previous data, M1 tES, especially using tDCS, does not seem to induce an analgesic effect or to reduce itch sensation in patients with burn injury [14]. It does not seem to have an effect on psychosocial symptoms, while stimulating the prefrontal cortex seems to have a more straightforward approach to improve such factors (Fig. 2).

Techniques such as tDCS, tACS or other NIBS tools have several advantages as well as some limitations. In our opinion, especially in the burn population, one of the main advantages is the non-pharmacological nature of tES. While opioids remain the cornerstone of pain management in the burn population [115]; given the risk of addiction, alternatives to pharmacological treatment are necessitated. tES represents a safe, inexpensive, and well tolerated modality as compared to other treatment strategies [116]. Mechanistically, NIBS techniques have the potential to modulate specific brain areas depending on the underlying symptoms to treat, via long-term potential and depression-like plasticity mechanisms [117–119]. However, currently this technique typically involves administration by trained staff under clinical supervision, requiring the administration of tES to take place in research facilities or hospitals. In addition, dosing is an important parameter as the duration of the effects is thought to be linked to the duration of tES application. Repeated sessions may have cumulative effects leading to long-lasting clinically relevant effects, as shown in previous studies evaluating the effects of tDCS in psychiatric [120], motor [121], and pain conditions [122]. Recently, some studies have utilized home-based tDCS devices with promising results and, most importantly, with no side-effects [123–125]. Thus, home-based supervised sessions, as recommended by Charvet and colleagues [126], could be an alternative to facilitate tDCS and tACS implementation and reduce attrition rates as

often observed in clinical trials of long duration [127], as well as to promote long-lasting tES-related effects. Besides the number of sessions, the intensity of stimulation is another parameter to take into account. Recent evidence has shown that 4mA tES is safe and can potentially induce stronger neurophysiological effects, and thus stronger behavioral effects too [128,129]. However, a direct link between clinical effects and higher intensities of stimulation still needs to be proven.

5. Conclusion

Non-invasive brain stimulation (NIBS) techniques represent a valuable alternative to pharmacologic interventions in the management of chronic neuropathic pain, psychiatric morbidities and sleep disturbance. However, current literature on NIBS in burn for treating these and other associated symptoms remains limited and future trials are merited to investigate the efficacy of this approach. Specifically, home-based supervised devices may be utilized in order to limit attrition rates as observed in previous trials [127]. Our review of the neural circuitry involved in post burn symptoms and suggested targeted areas for stimulation provides a spring board for future study initiatives. Given the significant impact of these symptoms on survivors' lives, definition of these target areas allow for focused studies of treatment of these symptoms and eventual improved quality of life. Based on the importance of the prefrontal cortex in the emotional component of pain and its implication in various psychosocial symptoms, this region may represent the most promising treatment target.

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Conflict of interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.burns.2020.06.005>.

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