Chapter 7

Neurostimulation Techniques for the Modulation of Pain

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Abstract

Non-invasive brain stimulation (NIBS) is increasingly proposed as a therapeutic intervention for many neurological and psychiatric disorders, including pain, depression, obsessive compulsive disorder, and anxiety. While neuromodulation as an intervention for pain relief has a well-established scientific basis, evidence is largely restricted to invasive stimulation that targets the spinal cord. Novel non-invasive methodologies instead predominately target cortical processing of pain and thus raise interesting questions about how the most effective pain relief can be achieved. Functional magnetic resonance imaging (fMRI) studies show a widespread and distributed activation of brain areas during pain. This diverse activity is often referred to as the "pain neuromatrix" and can lead to the proposal for different possible target areas for pain relief. Neuromodulation could target brain regions of pain processing areas responsible for sensorimotor processing or alternatively regions responsible for the affective and evaluative aspects of the subjective pain experience. The chapter addresses the different approaches currently taken in the use of non-invasive neuromodulation for altering pain both in an experimental setting and the challenges involved in the translation of these techniques to a diverse range of chronic pain conditions.

Keywords: pain, neurostimulation, transcranial magnetic stimulation, transcranial direct current stimulation, quantitative sensory testing

1. Introduction

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. Nociception is an indispensable survival mechanism designed to minimize tissue injury, observed across species from the simplest invertebrate

model systems. Its critical function as a sense for survival is reflected by its emergence early developmentally. In all animals, the characteristic perception of nociceptive stimuli is rapid reflexive movement away from the source of the noxious stimulus (nocifensive behavior) and autonomic responses that optimize the ability to escape from threats [2]. In humans, pain encompasses not only these sensorimotor responses but critically also the cognitive evaluative component, and the IASP definition encompasses the subjectivity of the pain phenomenon.

Chronic pain represents a significant health burden worldwide with over 1.5 million people suffering from chronic pain globally [3]. Nearly 20% of those in Europe are believed to be in chronic pain, and lifetime prevalence of chronic pain worldwide has been put as high as 55.2% of the population [4, 5]. The experience of pain is known to have a substantial detrimental impact on an individual's quality of life and mental health status. Extensive research has documented the high correlation between pain and mental health difficulties, not just within clinical cohorts but also in community-based studies [6]. Pain can therefore be seen as an important risk factor for the development of psychiatric conditions, for instance, depression. Furthermore, there is a reciprocal nature to the interaction, with depression likely to exacerbate the individual's experience of pain [7]. Overall, the consequence is not just on the individual but also the societal economic burden of pain will be further compounded by the economic burden of the concomitant mental health difficulties of those experiencing it chronically.

2. Pain and pain processing

Noxious stimuli are detected by the free endings of pseudounipolar neurons (Aδ or C fibers) which project to the dorsal horn of the spinal cord to synapse with second-order neurons in laminae I–II and V–VII [2]. Type I small-diameter thinly myelinated Aδ fibers respond to strong mechanical stimuli; type II Aδ nociceptors respond to noxious thermal stimuli; unmyelinated C-fiber nociceptors respond to thermal, mechanical, and chemical stimuli [2]. Neurons of laminae I and V relay signals along the spinothalamic and spinoreticulothalamic tracts to supraspinal sites including the thalamus, parabrachial nucleus, and amygdala and to higher cortical centers such as the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), dorsolateral prefrontal cortex (DLPFC), and primary motor cortex (M1). Taken together, the combined activity of both cortical and subcortical regions that form a distributed brain network associated with pain processing is referred to as the pain "neuromatrix" [8]. The ventroposterior lateral and medial nuclei of the thalamus, S1 and S2 are concerned with the sensory-discriminative component of pain, encoding location, and duration of pain, whereas the medial nuclei of the thalamus and anterior cingulate cortex (ACC) are regions suggested to underlie the cognitive-evaluative aspect of pain, including pain-related learning [2]. Descending pathways pass through the periaqueductal gray matter (PAG), which has been long established as important in the endogenous modulation of pain via early electrical stimulation studies [9]. The PAG is part of a central circuit that controls nociceptive transmission at the level of the spinal cord dorsal horn via a relay in the rostral ventromedial medulla (RVM) [10]. The PAG receives direct projections from a number of medial prefrontal cortical areas, including the ACC, the amygdala, and the hypothalamus [11–14], with a primary output to the RVM critical

to descending pain modulation. The PAG-RVM system's critical role in the central control of nociception has been demonstrated by lesion studies [15]. Taken together, these studies indicate that the intensity of pain will be the consequence and composite of interactions between ascending nociceptive inputs and descending antinociceptive controls. Dysregulations in any aspect of these networks may underlie vulnerability factors for the development of chronic pain [16].

2.1. Pain and the chronification of pain

While acute pain is highly functional to survival and an adaptive sense that is protective against tissue damage, the mechanisms behind the development from this protective function to the maladaptive disease of chronic pain in a proportion of individuals remain elusive. Chronic pain is defined as pain that persists for 3–6 months after the initial nociceptive stimuli [17]. Methodologies that have potential to predict individual patients with pain who are at risk of developing chronic pain would be particularly valuable at helping to understand the physiological mechanisms behind this very detrimental disease process. Recent research suggests that the use of computational machine learning methods to analyze large data sets of medical and demographic characteristics collected from patients who develop chronic pain patients may aid understanding of the risk factors underlying chronification and a possible chronic pain phenotype [18]. This is an interesting concept, though ultimately dependent on the relevant predictors of pain chronification being in the analyzed data set. For instance, while there has been recent interest in the use of quantitative sensory testing to characterize individual differences in pain sensitivity, thorough assessment of pain thresholds across a variety of modalities, this is by no means standard. That limitation aside, greater understanding of pain chronification is essential for the development of interventions for chronic pain and increased understanding of how to effectively disrupt the transition into a disease state. In the future, the inclusion of larger data sets will inevitably increase the predictive value of this emerging technique.

Chronic pain is characterized by increases in neuronal excitability leading to increased pain perception. These increases in excitability are believed to occur both peripherally and centrally, factoring into the overall elevated perceived pain. To date, research has predominately focused on spinal cord mechanisms. This perhaps is somewhat related to availability of appropriate animal models and the existing strong scientific basis. However, it is well established that spinal cord excitability can be modulated by descending pathways. Given the role of descending pathways in modulating excitability in the spinal cord, the input and impact of a wide range of cortical areas in perceived pain should be systematically considered and characterized. These cortical areas will not just include those directly related to sensorimotor processing but also encompass those areas important for the cognitive evaluative and emotional response to pain. NIBS techniques may provide a tool that can enable further insight into the mechanisms of pain processing from periphery through to cortex that may in turn reveal potential therapeutics for the treatment of chronic pain conditions.

Further, pain is categorized by the IASP as either neuropathic or nociceptive [19]. Neuropathic pain is a pain that is caused by a disorder of the somatosensory system and typically leads to symptoms that include hyperalgesia, allodynia, and pain in the absence of stimulation. Nociceptive pain is a pain that arises from damage to non neural tissue via the activation of

nociceptors. Another consideration is that although there is a broad distinction into neuropathic and nociceptive pain, there can be overlap in the two forms of pain, as well as the fact that pain can arise from a vast range of different underlying pathologies.

3. Neurostimulation for pain modulation

The use of electricity to alleviate pain has a long history, with the reported use of the electric emissions from the Nile catfish for pain relief in 3100 BC. Although there has been use of electrical stimulation continually, the groundbreaking gate control theory of Melzack and Wall published in 1965 changed the field and provided a strong basis for the design of appropriate interventions [20]. The theory proposes that the balance of activation between small- and larger diameter fibers determines the level of pain signaled. Small-diameter C fibers will open the "gate," and Aβ fibers (that signal innocuous touch), having a larger diameter, will close the "gate." Due to differences in the threshold of activation of these fibers in response to imposed electrical stimulation on a mixed nerve, a simple intervention to shift the balance of activation is possible. Neuromodulation of pain through electrical stimulation of implanted electrodes has substantial supportive evidence since its initial introduction in spinal cord stimulation (SCS) in 1967 [21] and is accepted as a standard form of treatment for intractable chronic neuropathic pain. Many of these implantable neurostimulation devices were adapted from the design of cardiac pacemakers, and their design and stimulation parameters have not changed substantially since their initial introduction. However, differences do exist among SCSs; for instance, some are based on tonic stimulation, whereas others on burst stimulation, and the stimulation frequency can be varied.

Other invasive stimulators have targeted pain pathways in the brain to alleviate pain, often utilizing the knowledge of role of the thalamus as having a critical role in sensory processing. Deep brain stimulation (DBS) has been applied to different thalamic nuclei, including the ventral posteromedial sensory nuclei and ventral posterolateral sensory nuclei and the centromedian-parafascicular intralaminar region. There is widely varying reports of the effectiveness of DBS of the thalamus but with the strongest response believed to be in patients with neuropathic pain [22]. DBS has also included stimulation of the ACC, with the aim of reducing the affective component of chronic pain, and this has been shown to be effective within small studies [23].

The primary motor cortex (M1) was the first cortical target that was proven to be efficacious in chronic pain treatment [24]. Motor Cortex Stimulation (MCS), where epidural electrodes are implanted has been shown to be a particularly useful intervention for neuropathic pain that is not responsive to pharmacological interventions [25, 26]. The primary motor cortex (M1) is somatotopically arranged and receives inputs from three main sources. These are [1] the peripheral body via the thalamic relay nuclei-somatosensory cortex system, from the premotor cortex and from the sensory association areas of the cortex; [2] the basal ganglia; and [3] from the cerebellum. Therefore, there is considerably overlap with motor processing areas and those associated with the pain neuromatrix. It is believed that cathodal MCS is associated with an indirect stimulation of pyramidal neurons via interneurons, whereas anodal MCS is

associated with a direct stimulation of pyramidal neurons. The indirect activation is believed to be optimal for MCS analgesia.

Invasive neuromodulatory devices have been the subject of research for much longer non-invasive neuromodulatory techniques, including randomized controlled trials. By reason of their very invasive nature, and obvious ethical constraints, the effectiveness and consequences of SCS, MCS, and DBS have only be assessed in patients and not experimentally investigated in healthy volunteers, which may have limited the development of different stimulation protocols. Therefore, unlike these invasive stimulators, NIBS techniques potentially enable another important distinction to be considered, the difference in response to neuromodulation in chronic pain patient groups compared with healthy individuals exposed to experimental pain or experiencing acute pain.

4. Functional magnetic resonance imaging (fMRI) and chronic pain

Functional magnetic resonance imaging (fMRI) was first used in the area of pain in order to demonstrate the brain areas responsible for pain perception and part of the pain "neuromatrix" [28]. Subsequently, differences in the structure and function of pain patients compared with healthy controls have been observed through fMRI of experimental pain in both groups [29]. Chronic pain patients show similar activation but with a decrease in thalamic and ACC activation. Activity in the prefrontal cortex (PFC) typically shows an increase in clinical pain conditions. This preferential activation of PFC in chronic pain conditions advocates that chronic pain states have stronger cognitive-evaluative aspect of pain [16].

As well as functional changes, structural changes have been observed through MRI in patients experiencing long-term pain. Chronic pain patients are found to show neuronal loss in significant pain pathways including the thalamus and the lateral prefrontal cortex [30]. Fibromyalgia, a patient group with a particularly complex range of sensorimotor symptoms, shows gray matter loss in the DLPFC [31], and this is believed to be consistent across different chronic pain patient groups. For instance, patients with chronic lower back pain also show reductions in gray matter in distributed regions of the pain "neuromatrix," including DLPFC. This decrease in gray matter also occurs in prolonged pain states in the general population as well as clinical groups [32], and on resolution of persistent pain, for instance when a patient with knee osteoarthritis (OA) undergoes knee arthroplasty, gray matter levels increase in parallel.

fMRI has also been used to demonstrate the effectiveness of neuromodulatory interventions, as well as the scope of the effect of stimulation. For instance, functional connectivity changes were observed in a group of neuropathic pain patients who had undergone SCS. After implantation, decreased connectivity was found between somatosensory and limbic areas of the brain, showing how central changes can be mediated by SCS [28]. Studies using combined NIBS/fMRI may provide interesting insights on the effect of neuromodulation protocols on changes in functional connectivity of the pain neuromatrix as has been done in other treatment interventions [33].

5. Noninvasive brain stimulation: Investigative and therapeutic uses

NIBS is well established as a tool to study the physiology of the CNS, elucidate functional anatomy of specific brain regions and explore brain network organization and plasticity [34]. However, currently the application of NIBS to pain research is much more recent, although this is a rapidly expanding field [35]. The most commonly used forms of NIBS that aim to modulate neuronal plasticity are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), with the techniques rapidly expanding to variations on these methods. Transcranial alternating current stimulation (tACS) is a particularly exciting new method where an alternating current is applied with the aim of enhancing network oscillations at frequencies close to the stimulation frequency [36]. Therefore, the rationale behind the tACS technique is that it may lead to pain modulation via the alteration of specific rhythmic activity known to be associated with pain processing [37], but currently, there are only a few experimental studies applying this technique to experimental or clinical pain. For all of these methodologies, the noninvasive nature, relatively low cost, and well-established safety and tolerability make these neuromodulatory techniques potentially important tools both for neurophysiological studies and to aid the development of long-term therapeutic interventions [38].

5.1. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has both neuromodulatory and neurostimulatory properties. The technique, first introduced in 1985, has subsequently been widely used as a tool to study cortical brain areas, particularly motor cortex. The technique involves a stimulating coil of wire positioned over the desired brain target area, with a brief pulse of current passed through the coil, so generating a magnetic field which penetrates through the skull with negligible attenuation. The rapidly changing magnetic field induces a secondary current in the subject's brain, thus stimulating neural tissue via the depolarization of neurons [34]. Thus the technique overcame many of the problems associated with electrical stimulation, where the skull provides a barrier. With an appropriate figure of eight coil [39], TMS can be used to stimulate precise regions, such as the hand area of the motor cortex (C3). The motor cortex is a particularly good target for TMS usage in the absence of neuronavigation software packages that guide coil positioning over the appropriate brain target area as single-pulse TMS eliciting motor evoked potentials (MEPs) that can be recorded using electromyography (EMG), which enable the determination that the correct cortical area has been stimulated. MEPs are further used to determine the stimulation intensity required in an experimental protocol via the measurement of motor threshold and the quantification of changes in corticospinal excitability [34, 40, 41].

Repetitive transcranial magnetic stimulation (rTMS) refers to the application of a train of pulses and dependent on the frequency acts to suppress or facilitate the activity in an underlying brain area. The stimulation of the motor cortex with low frequencies (1 Hz or less) is associated with a decrease in corticospinal excitability, whereas higher frequencies (20–50 Hz) have been associated with an increase in excitability [42]. It has been noted that these effects are somewhat inconsistent, thereby limiting its therapeutic applications [43]. A possible reason behind this is that rTMS is dependent on stimulation parameters other than

frequency, and baseline corticospinal excitability of the targeted brain area is a critical parameter in determining the consequence of rTMS [44].

5.2. Pain modulation through repetitive transcranial magnetic stimulation of motor cortex

Given the known efficacy of MCS for pain relief, the primary motor cortex was an obvious initial choice of target for NIBS interventions. Further given the corticospinal tract is known to have non-motor functions, that include a role in nociception, the stimulation could have an effect on this pathway [45].

High-frequency rTMS of the motor cortex has been shown to be efficacious in the treatment of pain [35, 43, 46, 47]. Significant reductions in pain ratings occur following high-frequency stimulation and these stimulation effects lasting from several minutes up to 8 days and even longer after multiple rTMS sessions. Stimulation of the motor cortex with high-frequency rTMS showed significantly increased pain thresholds with regard to cold thermal stimuli, meaning rTMS reduced the temperature at which the cold sensation became painful [40]. This demonstrates that rTMS not only can modulate chronic pain, but also experimentally induced acute pain.

Evidence for M1 rTMS for pain relief is mounting, but there is still a shortage of large studies, and the duration of the neuromodulatory effect is not well established. Technical considerations with coil positioning may alter the effectiveness of rTMS as an intervention for pain relief which may not be completely controlled for in different studies. In rTMS, the coil is typically placed over M1 in an anteroposterior orientation which is associated with transsynaptic activation of pyramidal neurons, and this placement is believed to be optimal for analgesic effects compared with the placement of the coil in a lateromedial orientation, similar to findings with MCS [27]. Further, there is evidence that when the electrodes are placed over the somatotopic M1 region of the painful area, that optimal analgesic effect can be obtained [27].

The mechanisms behind M1 rTMS-facilitated analgesia are still not established. Previous research on implanted MCS has suggested that the modulation of pain is related to the inhibition of thalamic activity. M1 rTMS could modulate the pathways from the insula and orbitofrontal cortex to the posterior thalamus in order to upregulate these pain thresholds [48]. The modulation of pathways from the insula could be particularly significant, given recent research suggesting that the insula act as the cortical generator of pain perception, integrating sensory and affective components of pain [2].

The neurochemical mediation of the neuromodulation is still uncertain. There is evidence that the endogenous opioid system may be responsible. Additionally, the activation of GABA (*gamma*-Aminobutyric acid)-ergic and glutamatergic pathways may be critical. For instance, high-frequency rTMS is believed to restore defective intracortical inhibition, a measure associated with impairments in GABAergic neurotransmission in patients with chronic pain [47]. Glutamate N-methyl-D-aspartate (NMDA)-receptors are also thought to be involved in rTMS neuromodulatory effects, in that there was observed a decrease in analgesic effects after the administration of the NMDA antagonist, ketamine [49]. This supports the ability of rTMS to induce synaptic plasticity via long-term potentiation (LTP) and long-term depression (LTD) like mechanisms.

5.3. The dorsolateral prefrontal cortex

A second cortical target that has been investigated by NIBS is the DLPFC [50] The DLPFC is connected to the orbitofrontal cortex and to other areas of the pain "neuromatrix," in particular the thalamus and dorsal caudate nucleus. Evidence from multimodal studies, including neuroimaging, TMS, and tDCS, suggests that DLPFC is important in the affective modulation of pain [51–55]. The DLPFC has shared connectivity with regions associated with sensorimotor processing and monitoring of motor performance. This connectivity highlights the potential importance of the DLPFC as a target for neurostimulation for the modulation of pain [56]. Further, in addition to its possible ability to modulate the sensory-discriminative aspects of pain perception and experience, DLPFC has reciprocal networks within the ventromedial prefrontal cortex supporting the integration of memory and stimulus characteristics. Additionally, it has been found that increased activity in the DLPFC is associated with decreased pain intensity and unpleasantness.

High-frequency rTMS of the DLPFC has been shown to alleviate neuropathic pain in patient groups [57]. Experimentally, the effects of low-frequency rTMS on both left and right DLPFC have also been reported where it was found that stimulation inhibited placebo analgesia, and so increased heat pain ratings [51]. This finding related to placebo analgesia highlights some of the difficulties involved in assessing the efficacy of NIBS interventions.

Differing mechanisms have been proposed for the alleviation of pain through increased activity in the DLPFC, one is that it is able to activate descending modulatory pathways through the periacqueductal gray, whereas an alternative mechanism was via modulation of thalamic activity as has been proposed by fMRI studies [58]. There is also a proposed role for the DLPFC in terms of the anticipation of pain, which could provide some explanation for placebo-related alternations in pain thresholds. One of the difficulties that arises in the comparison of active treatments to placebo is the possibility of an analgesic response to the placebo itself, which may be mediated by endogenous opioids [59, 60]. With this in mind, the ability of NIBS to modulate the placebo effect is in itself interesting.

5.4. Neurophysiology of tDCS

tDCS is a non-invasive technique, where weak direct current (<2 mA) is applied on the scalp for 10–20 mins using large saline-soaked sponge electrodes. In contrast to TMS, tDCS is neuromodulatory rather than neurostimulatory and as such influences spontaneous neuronal activity by modulating resting membrane potentials [61]. Animal studies have demonstrated that anodal tDCS depolarizes membrane potentials and increases neuronal firing rates and excitability, whereas cathodal stimulation hyperpolarizes membrane potentials, leading to decreased excitability [62]. Modeling techniques suggest that these short-term effects may be mediated by glia, with tDCS modulating glial transmembrane potential that may in turn alter glial regulation of potassium or glutamate homeostasis [63]. Due to technical difficulties, experimental evidence to examine the precise effect on glia is limited. Both anodal and cathodal long-term effects have been attributed to N-methyl-D-aspartate (NMDA)-receptor activation; the NMDA-receptor antagonist dextromethorphan has been reported to suppress the aftereffects of anodal and cathodal tDCS [64, 65]. Further, studies using magnetic resonance spectroscopy have reported

that anodal stimulation inhibits neurotransmission by the inhibitory neurotransmitter GABA [66], whereas cathodal stimulation inhibits neurotransmission by the excitatory neurotransmitter glutamate [67, 68]. While the precise mechanisms remain elusive, recent research in animal models suggest that weak electrical stimulation acts as a modulator, rather than an inducer of synaptic plasticity with its effects highly dependent on endogenous synaptic activity [69].

5.5. High-definition transcranial direct current stimulation

High-definition transcranial direct current stimulation (HD-tDCS) is a technique used to increase the spatial focality of tDCS by using <12 mm diameter ring electrodes [70]. As an investigative tool, HD-tDCS holds several advantages over conventional tDCS. Neuroimaging and modeling studies have demonstrated that conventional parameters induced neuromodulation extends outside the area covered by the target electrode [2, 71]. In addition, the largest current densities for conventional tDCS may not be produced directly under the target electrodes [70]. In comparison to the diffuse effects of conventional tDCS, HD-tDCS enables a more targeted approach to neurostimulation, potentially avoiding modulation of confounding brain regions and permitting isolation of certain pain processing pathways [72].

The predominant montage for HD-tDCS is a 4x1 array configuration consisting of five ring electrodes: 1 "active electrode" placed over the target area surrounded by a ring of 4 "return" electrodes placed equidistant from the central electrode [71]. This 4x1 montage increases intensity and focality of the stimulation, with peak stimulation situated under the central electrode. Further, the montage also allows for depth, focality, and intensity of stimulation to be titrated depending on the ring diameter [73]. In addition to improved focality, HD-tDCS has lower observed adverse effects, including less itching and scalp discomfort and with the further advantage of a longer duration of neuromodulatory effects [3]. Recent multidimensional electrode arrays are now available but, thus far, very little research has been conducted.

5.6. Pain modulation using transcranial direct current stimulation

Multiple types of experimental pain have been used to study the effects of NIBS on nociceptive signaling in healthy human subjects [74]. tDCS of M1 produces sustained analgesia in chronic migraine, fibromyalgia, and orofacial pain [38]. Currently, the level of evidence for the use of tDCS in neuropathic pain is currently lower than that for rTMS [17, 75]. Similar to the effect of rTMS on DLPFC, there is also evidence that tDCS of the DLPFC modulates pain. For instance, anodal tDCS of the left DLPFC has been shown to increase electrical pain thresholds [76]. There are currently fewer studies targeting DLPFC, but future work on this area is of clear interest.

The mechanisms by which tDCS modulates pain processing have not yet been fully elucidated and likely differs between target brain regions. Anodal M1 tDCS increases cortical excitability [62] that may result in disinhibition of glutamatergic M1 neurons that activate sensory gating mechanisms in the thalamus via corticothalamic projections, reducing incoming nociceptive information to somatosensory cortex [77]. Alternatively, stimulation of M1 may stimulate GABAergic neurons to restore functional intracortical inhibition in chronic neuropathic pain [47]. In addition, tDCS of M1 may directly increase opioid release [46, 78].

5.7. Transcranial direct current stimulation priming of repetitive transcranial magnetic stimulation

The physiological connectivity and neuronal plasticity of the M1 are two important factors that have been overlooked in the development of NIBS pain modulation protocols in the past. The use of tDCS-primed/preconditioned rTMS stimulation has been suggested as a more robust form of intervention [79, 80]. When tDCS was used to augment background motor corticospinal excitability, the cortical plastic changes induced by subsequent rTMSs were standardized. It has been demonstrated that weak 1 mA tDCS reversed the usual effects of rTMS on corticospinal excitability [81]. That is, preconditioning using a session of cathodal tDCS modified the expected suppressive effect of low-frequency rTMS and led to an overall cortical excitation, whereas anodal tDCS resulted in an overall motor cortical inhibition. This manipulation of effects is based on the conceptual form of brain plasticity, "homeostatic plasticity" [82]. This protocol has been applied to the modulation of pain, and weak tDCS (1 mA) was used to "precondition" the brain to enhance the effects of subsequent stimulation via low-frequency rTMS (1 Hz) on the modulation of thermal sensation, thermal pain thresholds, and pressure pain thresholds, thereby producing a form of analgesia [83, 84].

5.8. Dose effects of neuromodulatory interventions

The physiological mechanism underlying the effects of tDCS remains controversial. Unlike pharmacological interventions for pain relief, where the appropriate dosage is carefully considered, the issue of "dosage" of neurostimulation has been somewhat neglected in the literature [85, 86]. Recent research has been working toward establishing factors responsible for variability in tDCS effects; such as the positioning of the electrodes on the scalp as well as the intensity and duration of the stimulation. This is best demonstrated in studies regarding application to the human motor cortex, where they attempt to direct the current to strictly follow the orientation of axons and/or dendrites in the induced electrical field [61]. Recent studies employ current flow models with defined montages [86] and use improved electrode positioning through the use of caps based on the international 10–20 positioning system [84].

Interestingly, there is evidence that when the electrodes are placed over the somatotopic M1 region of the painful area, optimal analgesic effect can be obtained [27]. This could potentially explain some of the differences in treatment efficacy reported in rTMS studies in pain patients where the exact target of the stimulation in relation to the painful area is not controlled for or appropriately selected. A further complication to this is the variation in chronic pain conditions as to the extent of spatial localization of the perceived pain.

TMS has a much longer history of research than other NIBS techniques. However, there has been only slow development in stimulator design. An interesting recent development has recently occurred in TMS that may improve future therapeutic interventions. Until recently, there has been a complete lack of complete experimental control over the stimulation pulse shape in TMS. It will be interesting to see the emerging literature as new devices develop that examine the differential impact of altering stimulation pulse widths and waveforms via

controllable TMS (c-TMS) [87]. These devices may be critical in optimizing TMS to maximize analgesic effects.

5.9. Combining neuromodulation with pharmacological interventions

In addition to independent efficacy, it may be that NIBS can work in a synergistic fashion with pharamacological interventions for pain relief. This question has been examined with regard to stroke recovery in large randomized control trials in an extensive research network. A number of recent studies have combined drug interventions with rTMS in rehabilitation in patients after stroke [88]. Interesting questions can be raised as to whether drug action can prime the brain and enhance the effect of TMS or vice versa. The same approach should be systematically carried out in patients with chronic pain conditions (27).

6. Challenging issues and inconsistencies in NIBS

NIBS is rapidly emerging as an intervention proposed for wide-ranging neurological and psychiatric disorders. However, tDCS studies have recently been scrutinized due to reported high degree of variability in effectiveness in published studies to date [89]. Evidence on the therapeutic use of both tDCS and newer methodologies like tACS are currently very limited, and the optimal parameters for use have yet to be fully elucidated. Many have suggested that there is a currently a general lack of understanding of the mechanisms by which these interventions are effective. However, tDCS has several advantages compared to the better investigated rTMS including ease of use, portability, and reduced expense [90], which support further investigation into the potential of tDCS in the treatment of pain.

Despite this, there is increasing evidence that NIBS are effective in the modulation of experimentally induced pain [91] as well as chronic pain conditions although the caveat to this is that there is reported variability in responsiveness across studies and individuals in both experimental and clinical studies. This efficacy of NIBS for experimental pain challenges the previously held understanding that neurostimulation devices act solely by interfering with the long-term maladaptive plasticity associated with chronic pain. Instead, it points toward a general lack of sufficient mechanistic understanding as to how NIBS modulates pain and how this modulation differs across individuals [92]. Moves toward characterizing differing individual "pain phenotypes," based on a battery of quantitative sensory testing, may provide insights into why some individuals respond to NIBS [7]. The use of protocols designed to give insights into an individual's endogenous descending modulation such as conditioned pain modulation (CPM) [93] may also be useful in conjunction with NIBS, in the same way that these protocols have been used when differentiating groups that respond to pharmacological treatment interventions. Another possible reason for the variability of the effects of rTMS on acute pain could be differential effects on each pain modality. For example, it is possible that rTMS may influence A- δ –fiber-mediated and C-fiber-mediated pain differently [94].

7. Is optogenetics the future of noninvasive brain stimulation?

Optogenetic techniques, where light-activated ion channels from microbial opsins are expressed in neurons enabling their activity to be controlled remotely by light, are rapidly increasing our understanding of neural circuits [95, 96]. In animal models, the technique has been used to investigate pain processing pathways; for instance, optogenetic activation of the prefrontal cortex has been found to lead to antinociceptive effects. This study highlighted the importance of a previously unexplored prefrontal to nucleus accumbens pathway that may in the future provide insights into treatment interventions for intractable pain [97]. As the field expands, optogenetic techniques are likely to lead to substantial increases in our understanding of pain processing by their use in animal models. In addition to the contribution to basic science, optogenetics has been predicted to have translational potential as a therapeutic neuromodulatory intervention for neurological disorders. One of the current limitations of the use of this technology in humans will be in how to safely deliver the channelrhodopsin (ChR2) gene to the targeted neuronal population. Nonetheless, it is likely that progress will occur very rapidly in this field due to its vast therapeutic potential [98].

8. Conclusion

The use of the NIBS for the relief of pain is a relatively new field and provides an exciting opportunity for neuromodulatory interventions to move to targeting cortical areas rather than traditional spinal cord stimulation. NIBS opens up the opportunity to fully probe the contributions of the widespread brain areas that are thought to be associated with pain processing in the pain neuromatrix. With the associated risk factor of mental health difficulties in chronic pain patients, this is particularly interesting as NIBS introduces the possibility of targeting cognitive-evaluative aspects of pain. Further NIBS allows experimental studies in healthy participants, as well as patient intervention, allowing the investigation of the neuromodulation of pain processing in health and disease. Taken together, these studies provide the potential for greater understanding of the role of descending modulation in pain perception and how this modulation is influenced by chronic pain. There is a clear need to look toward NIBS for future therapeutic interventions for chronic pain as there are currently a number of challenging chronic pain syndromes that are often refractory to conventional pharmacological therapy [3]. With the increasing numbers seeking treatment to pain associated with chronic disease and injury, the development of safe and effective forms of treatment is crucial in terms of both public health and the economy.

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Conflict of interest

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