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Chapter

From Mechanisms to Analgesia: Towards the Use of Non-Invasive Neuromodulation for Pain Relief in the Clinic

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Abstract

The use of electricity for analgesic effects has a long history and yet currently neuromodulation devices based on electrical stimulation are typically restricted to being a last resort intervention for pain patients after the failure of pharmacological treatments. Whilst spinal cord stimulation is an established intervention for intractable neuropathic pain, the use of neuromodulation for other forms of pain and targeting different aspects of pain processing is less well established. Non-invasive neuromodulation as part of a standard intervention for pain relief would be ideal for without long term treatment of a chronic pain condition as it would avoid the inevitable side effects associated with long-term use of pharmacological interventions or interactions between different drug treatments. This is particularly relevant as chronic pain can be associated with diseases that would require pharmacological treatment for the primary condition. However, there is currently both a deficit in understanding the mechanisms of the different non-invasive devices and also in how these devices may facilitate pain relief for specific conditions. This review will focus on the application of electric currents non-invasively to different sites for pain relief and outline the future potential of these technologies.

Keywords: pain, electric current stimulation, non-invasive neuromodulation, transcutaneous stimulation, tDCS, tACS, ta-VNS

1. What is neuromodulation? Why is pain a challenge?

Neuromodulation has been defined by the International Neuromodulation Society (INS) as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" [1, 2]. Neuromodulation has a wide range of possible clinical applications from the enhancement of vision, auditory function and the control of musculature, but the application to alleviate pain is perhaps one of the most challenging for the field. Whilst the efficacy of neuromodulation interventions, for instance for movement disorders, can be easily measured due to the many ways in which successful movement execution can be characterized,

and improvements in vision and audition measured via sensory detection thresholds, the efficacy of a potential neuromodulation intervention to alleviate pain is far harder to determine. Currently there is not an established biomarker for pain, and objective measurement of an individual's pain levels either before or after an intervention is difficult due to the subjectivity inherent in the pain experience.

Pain involves multiple processing regions from the periphery through to the brain and therefore, successful neuromodulation for pain relief has a number of possible targets. A clear premise of clinical neuromodulation is that pathological alterations in neuronal function are targeted, but for chronic pain these alterations can occur due to dysfunctions at a number of different sites within the multiple interconnected pain processing pathways. Additionally the mechanisms underlying the persistence of pain long after the initial injury, and the formation of a chronic pain state, still remain elusive. Pain, particularly chronic pain, is typically regarded as a human phenomenon, with other animals simply experiencing nociception; a stimuli that generates a reflexive response but without key aspects that encompass pain; that is without cognitive and emotional evaluative aspects.

Neuromodulation, particularly non-invasive neuromodulation, is a rapidly emerging field for therapeutic interventions and although the effects of stimulation are evident, many questions remain open; what patient groups will this technique be effective for?; what stimulation parameters should be used for optimum efficacy?; what is the most efficacious target for pain relief? Furthermore the mechanisms underlying neuromodulation has not been completely established. Therefore, taken together, the design of optimum neuromodulation protocols and targets for pain relief is an area that still requires development.

2. Importance of developing neuromodulation for pain relief

Chronic pain is a global health problem with both a high economic cost in addition to its substantial detrimental impact on quality of life [3]. Remarkably lifetime prevalence of chronic pain has been put as high as 50% of the global population [4, 5]. Chronic pain is the most common co-morbidity for a disease, with pain as the most frequent reason for seeking healthcare. Recently chronic pain has been recognized by the World Health Organization as a disease and included in the international classification of diseases (ICD-11) [6]. However, treatment interventions are lacking; pharmacological interventions providing inadequate pain relief with the mismanagement of opioids well documented as both increasing mortality and exacerbating pain. For neuromodulation to be an effective alternative for analgesia, an understanding of the mechanisms leading to pain conditions and the networks that enhance pain or inhibit pain is essential. For therapeutic benefit, neurostimulation techniques should modulate the nervous system in a non-destructive way with reversible effects that can be applied long term and have specificity to a targeted network. Further the intervention should be controlled dependent on individual patient requirements [7]. Recently a number of new non-invasive techniques have emerged; weak electric currents applied transcranially to cortical or sub-cortical site are proposed as interventions for a number of diseases that are associated with pathological alterations in neuronal excitability [8, 9], including chronic pain. Further the recent development of transcutaneous vagal nerve stimulation also offers therapeutic potential for some pain patients. Although these novel non-invasive interventions offer

promise, there remain areas of uncertainty with regards to how to optimize stimulation protocols and standardize their efficacy across individuals.

3. The anatomical substrates for pain: potential targets for neuromodulation

The sensation of acute pain originates from stimulation of nociceptors. Nociceptive input has different modalities; thermal, chemical or mechanical; that are all capable of causing pain. Receptor types and ion channels will differ dependent on the stimulus and intensity, but with free nerve endings transmitting the noxious information to Aδ and C afferents. The TRP channels for transduction of noxious temperature sensation are well characterized [10, 11], with less known about mechanical pain [12]. Myelinated, high velocity (20 m/s) Aδ fibers and un-myelinated, low velocity (2 m/s) and C fibers transmit nociceptive information from the periphery to the dorsal horn. Both Aδ and C afferent fibers terminate in the dorsal horn of the spinal cord, where afferent input is organized in the rexed laminae; finer diameter fibers terminate more laterally, and larger fibers more medially. Large diameter Aβ fibers conveying innocuous touch can modulate nociception transmission as formulated by the gate-control theory of pain. This theory represented a ground breaking advance in the understanding of the peripheral and spinal processing of nociceptive inputs that led to the development of therapeutic neuromodulation interventions [13]. There is transmission from the spinal cord via multiple ascending pathways; spinothalamic, spinoreticular, spinomesencephalic, and spinocervical pathways [14]. The thalamus is an important site of nociceptive transmission to different brain regions known to be involved in pain processing and interpretation. Additionally significant modulation of afferent input occurs at the thalamus that has led to the region being one of the first supraspinal areas targeted in neuromodulation interventions. The multiple cortical and sub-cortical regions of the brain that are involved in pain processing and modulation have become known as the pain neuromatrix [15], or the pain connectome [16]. Particularly critical to the modulation of pain is the descending pain pathways providing endogenous inhibitory control of nociceptive input.

Chronic pain typically is defined as pain that lasts 3-6 months, with the pain experienced no longer associated with a tissue injury. Chronic pain can result from defects in different sites of the pain processing pathways [17] and is often associated with both peripheral and central sensitization [18]. The pain processing network is known to be complex and distributed. In the brain, painful stimuli is known to lead to activation in diverse brain regions; including the frontal lobe, anterior cingulate cortex (ACC), primary motor cortex (M1), primary sensory cortex (S1), secondary sensory cortex (S2), insular; hypothalamus; nucleus cuneiformis; periaqueductal grey; rostral ventromedial medulla; as observed via fMRI studies [19]. The development of chronic pain is thought not just to involve neural changes but also alterations in glia [20]. These glial changes are thought to partly underlie alterations in pain transmission and the formation of chronic pain circuitry. Imaging studies show that chronic pain leads to structural and functional changes in multiple brain regions [21]. Chronic pain has also been reported to be associated with dysregulation of both the sympathetic and parasympathetic nervous systems [22]. Therefore, the potential targets for non-invasive neuromodulation for pain relief are diverse and could be within the central or peripheral nervous systems.

3.1 Primary motor cortex

Electrical stimulation of the primary motor cortex (M1) is long established as an effective treatment for pain. Originally this intervention was limited to invasive epidural electrode implantation, and so associated with the risk of surgery [23]. More recently non-invasive cortical stimulation has emerged as an interesting, effective, and promising modality in the investigation of novel approaches for pain relief [24]. The motor cortex represents a cortical region with high intra-cortical connectivity as well as connectivity to sub-cortical regions. There are a number of explanations for the efficacy of M1 stimulation [25]. M1- thalamic connectivity is thought to be particularly significant in neuromodulation effects [26]. Efficacy of M1 neuromodulation is also proposed to be due to inhibitory effects via the limbic, cortical and subcortical brain areas involved in descending modulatory pain control. Further M1 tDCS has been shown to reduce secondary hyperalgesia and enhances descending modulatory control [27].

3.1.1 Monitoring the efficacy of M1 stimulation

The measurement of pain in a clinical setting has been typically through visual analogue scales (VAS) and numerical rating scales (NRS). However many studies now include pain threshold testing via standardized quantitative sensory testing (QST) which involves testing across different modalities of nociceptive stimuli so that a pain modulation profile can be monitored pre and post treatment intervention [28]. MRI studies have examined resting-state functional connectivity alterations in pain patients before and after intervention with tDCS and found alterations in connectivity within pain processing areas that correlate with a reduction in pain in these patients [29].

Neurophysiological techniques have also been used to monitor changes in cortical excitability after the application of electric currents so that these changes may be correlated with pain measures. Increased excitability of the corticospinal tract (CST) as measured by the standard neurophysiological technique of motor evoked potentials (MEPs) have shown that increased CST excitability is associated with analgesic effects [30] and beneficial outcomes for patients [31]. Other neurophysiological measures that have been shown to have value include intracortical disinhibition. A number of studies have observed that there is a reduction in intracortical inhibition and an increase in intracortical facilitation, suggesting that motor cortex inhibition is dysregulated in chronic pain patients [32] and so providing a neurophysiological basis for monitoring efficacy of neuromodulation protocols.

3.2 Endogenous descending control of pain

It is well known that once a nociceptive stimuli has been identified, the typical response across all animals is rapid reflexive movement away from the source of the noxious stimulus combined with an autonomic response which acts to optimize the animal's ability to escape from threats. The periaqueductal gray (PAG) has a critical role in the response to threatening stimuli, both aversion and the autonomic response [33, 34]. The PAG is also a key component of the endogenous descending pain pathway [35]. It receives nociceptive input from spinal, subcortical and cortical inputs, and projects to the rostral ventromedial medulla (RVM) and also to cortical areas and the spinal cord. The initial rodent studies of PAG stimulation demonstrated a large analgesic effect subsequent to stimulation [36]. Subsequently, PAG stimulation has shown anti-nociceptive effects from rodents to man and is now known as an essential circuit for opioid based analgesia. However, it is also established that the PAG and descending pathways play a complex role in pain and can facilitate as

well as inhibit pain. Importantly, these endogenous descending pain pathways are thought to be defective in some patients, leading to chronic pain. To improve and develop neuromodulatory interventions it would be ideal to first characterize the integrity of the patient's descending modulatory pathway and subsequently monitor the effect of an intervention on this pathway. Two experimental observations using psychophysical methods are thought to enable important insights in the endogenous descending modulatory control and have generated interest in pain research. These are offset analgesia (OA) [37] and conditioned pain modulation (CPM) [38]. It would be useful if these methods could monitor the efficacy of neurostimulation protocols aimed at enhancing inhibitory pain pathways.

3.2.1 Offset analgesia

Offset analgesia (OA) is a phenomenon observed in both experimental and clinical studies [39]. OA is defined as a disproportionate reduction in pain after a very slight decrease in experimental pain stimulus intensity. The size of the OA effect is very large, with the effect thought to be over 250% when compared with equivalent increases in pain intensity [39].

The physiological mechanism and function of this phenomenon is not completely understood, but there is substantial interest in OA due to the apparent analgesia that it can convey in the presence of a previously painful heat stimulus. Additionally deficits in OA has been demonstrated in a number of different clinical group of chronic pain patients, and therefore a psychophysical OA protocol could be incorporated as part of a diagnostic protocol for chronic pain patients [40]. However, there is debate over whether OA could be used as a means to monitor the success of pharmacological interventions [41, 42] and suggests that this protocol requires reliability testing prior to use for the assessment of intervention efficacy. fMRI evidence has suggested that the PAG is activated during OA suggesting that the descending control pain pathway is important in the experience of this phenomenon [43].

3.2.2 Conditioned pain modulation

Conditioned pain modulation (CPM) represents the phenomenon of 'pain inhibits pain' and is thought to be the human counterpart to descending noxious inhibitory control (DNIC) that has strong electrophysiological evidence in rodent pain models [44]. Although DNIC was observed in rats in the 1970s, the human counterpart as observed through psychophysical methods is much more recent [38]. While there is increasing evidence that deficits in CPM can predict the development of chronic pain the reliability of the response has been questioned and there are a number of alternative protocols in the literature [38].

Patients with knee osteoarthritis have also been found to have defects in the descending pain control that can be characterized by defects in CPM. Further CPM paradigms have been used to monitor the effect of neuromodulation interventions on the endogenous inhibitory pathways in experimental pain in healthy participants [45] and clinical pain in Fibromyalgia patients [46]. As well as M1 stimulation influencing descending pain pathways it is possible that prefrontal stimulation may also modulate PAG due to the known connectivity [47]. Prefrontal tDCS is a common target for tDCS for pain modulation [25, 48], but not currently assessed in the context of descending pain pathways as monitored via CPM protocols. However patient studies using tDCS of the left dorsolateral prefrontal cortex have suggested efficacy is achieved via enhancement of descending pain modulation as well as known cognitive effects of this stimulation [49]. The link between PAG and cerebellar circuitry [50] may suggest that cerebellar tDCS could also influence PAG. Experimental pain studies have

explored the use of cerebellar tDCS as a target for modulating pain thresholds [51], but there are currently only a few studies.

3.3 Vagal nerve stimulation

The vagus nerve is a large tract originating at the brainstem and is known for its widespread innervation, targeting every major thoracic and abdominal organ [52, 53]. Vagal nerve stimulation (VNS) has similarly been shown to provide multi-systems effects, and thus useful for a wide range of disease interventions. The recent development of non-invasive vagal nerve stimulation; via transcutaneous auricular vagus nerve stimulation (ta-VNS); rather than the traditional cervical implantation; increases therapeutic potential of the intervention as it removes the need for surgery [54]. Due to the novelty of ta-VNS there is currently a lack of consensus over the optimal stimulation protocol [55]. Stimulation is typically of low amplitude current (~5 mA) with pulses of 250–500 μs with a frequency of between 10 and 25 Hz [54]. Recently a number of studies have made efforts to individualize the stimulation level based on perceptual threshold using sequential testing protocols.

There is increasing evidence that VNS has anti-nociceptive effects [56, 57]. Analgesia is thought to occur through both the inhibition of spinal nociceptive reflexes and ascending transmission. There is evidence VNS and ta-VNS also modulates ascending inputs in the brain by altered activity in pain processing regions as observed via fMRI [55, 58]. Further a recent study examined the brainstem fMRI response to a respiratory gated ta-VNS protocol (known as RAVANS). Interestingly this study found that stimulation led to greater blood oxygen level dependent (BOLD) responses in the PAG [59]. Further this study explored the use of different stimulation frequencies, with a frequency of 100 Hz showing increased responsiveness of PAG. This alteration to a key site for endogenous pain modulation provides additional support for the potential of VNS for pain relief. Opioid receptor antagonists are found to reduce the efficacy of VNS, indicating that there is an opioid based mechanism for analgesia. Further VNS is also widely thought to have anti-inflammatory effects [56]. These anti-inflammatory effects are proposed to be due to neural-immune interaction at the peripheral nerves [60], with electric stimulation of the vagus nerve triggering a neural-immune reflex via cholinergic anti-inflammatory pathways that dampen the inflammatory response to infection or tissue injury and suppress the release of pro-inflammatory cytokines.

4. Translation for patient pain relief?

Early studies using tDCS in patient studies have had variable success and lack strong evidence of treatment efficacy [61]. Initial randomized controlled trials of anodal tDCS to primary motor cortex (M1) as an intervention for neuropathic pain found the intervention to be ineffective [62]. However, recent studies provide support for tDCS of M1 as a treatment intervention for knee osteoarthritis [63], fibromyalgia [64] and inflammatory bowel disease [29]. There have also been randomized clinical trials using prefrontal tDCS demonstrating tDCS to be effective in pain reduction in patients with multiple sclerosis [65] and fibromyalgia [49] and also reduce post-surgical opioid use [66]. A recent meta-analysis of selected randomized controlled trials of tDCS for non-cancer pain included predominantly M1 tDCS but also left dorsolateral prefrontal tDCS [48]. The meta-analysis showed active stimulation was consistently better than sham stimulation with stronger evidence for the efficacy of anodal M1 tDCS [48]. However, overall there remain shortcomings in the current literature on tDCS in patient groups; the study numbers are

small; the tDCS protocols differ across studies; the patient groups are heterogeneous making meta-analysis challenging; and the study designs used inconsistent, with some studies favoring a cross-over design to a control group. For tDCS to become an established treatment intervention, large multi-centre randomized controlled trials with standardized protocols and patient cohorts are necessary.

Studies using VNS in patient groups report beneficial effects of this form of stimulation in patients with pain associated with inflammatory conditions, for instance rheumatoid arthritis or migraine. Indeed recent studies have provided strong support for the use of vagal nerve stimulation in arthritis patients [56]. The combination of anti-inflammatory effects of VNS [67] with the previously mentioned analgesic effects via the endogenous opioid system may explain the potential for this technique in these patient groups. In fibromyalgia, although the disease etiology is uncertain, patients are known to experience systemic inflammation and neuroinflammation, and so may be a patient group that particularly benefits from this intervention.

5. Methodology for translation of electric current stimulation to the clinic

Evidence for the efficacy of non-invasive application of electric currents in humans for neuromodulatory effects has been rapidly increasing, with many proposed applications, including pain. The potential applications explored have been extensive as the technique is easy to implement, cheap and well tolerated by participants. Additionally an interesting potential development of non-invasive neuromodulation interventions suggests the method is a viable technique for patients to use in their homes with remote monitoring [68]. However there is not currently a consensus on the optimal protocols and variability in effects across individuals have been widely reported. For translation to the clinic, systematic study into the effect of altering the amplitude and duration of the applied electrical current is essential. These parameters include; electrode montage when targeting a given area; size of the electrodes; magnitude of stimulation and duration of stimulation [69]. As with many therapeutic interventions key questions are; how can neurostimulation dose be determined?; how can treatment fidelity be ensured?; how can individual variability be controlled when determining dose?

5.1 Electrode montage in tDCS

In tDCS the stimulation electrodes are typically two saline soaked sponge electrodes; an anode and a cathode; that range from 25 to 35 cm^2 placed above the region of interest and the reference electrode is positioned at another cortical region [70]. Early studies with tDCS used a very simple electrode montage, with two electrodes of the same size often with the assumption that the effect of the active electrode would be independent of the placement and size of the second, reference electrode. For motor cortex stimulation the typical electrode montage is to have the reference electrode placed over the contralateral orbit. It has been suggested that anodal stimulation protocols can be optimized by having the cathodal reference electrode as a larger size, thus rendering it functionally inert [71]. Another montage option has been the selection of an extracephalic reference electrode; typically the deltoid or buccinator muscles. Regardless of site used the montage of the two electrodes will inevitably impact on the regions where brain modulation will occur due to stimulation. Further the different forms of electrodes now available will also influence the applied stimulation as it is known that the electrode-skin interface has variable impedance that will be dependent on a number of factors that lead to variability in the delivered current. Modern

stimulators are current controlled, but some earlier studies are voltage controlled leading to the current that reaches the scalp being dependent on differences in impedance thus leading to greater variability and difficulty in making comparisons across studies.

5.2 Modeling current flow in tDCS

One limitation of tDCS is that the sites of stimulation are typically identified based on the cranial landmarks of the 10-20 system for EEG electrode placement. However individual differences in brain anatomy will result in electrode placement that may not correspond exactly to the intended target site of stimulation. M1 stimulation can be improved by identifying the individual's motor hotspot via transcranial magnetic stimulation (TMS) before electrode placement, but currently this is not typically included in the protocols for tDCS studies for pain relief. Recently current flow diagrams have been developed and are regarded as critical to the optimal administration of tDCS [72]. Ideally these predictions of the current flow are adapted to the specific anatomy as recorded via magnetic resonance imaging (MRI). Implementing tDCS in this way may help to control for some of the observed inconsistency in the effects of tDCS across populations [73]. This may be particularly important in some patient populations; recent work has further suggested that brain atrophy may also impact of the flow of current [74]. Given the observation of structural changes in the brain of chronic pain patients this may be problematic [22]. This may to some extent be ameliorated by individualized electric field models that can optimize tDCS dosage for patients [75, 76]. Current flow modeling also enables tailoring the dose to electrodes of different sizes, including high-definition transcranial direct stimulation protocols with smaller electrodes arranged in more complex montages to facilitate more focused effects [77, 78]. Additionally the current flow modeling may be able to facilitate the use of non-invasive neurostimulation techniques to deeper brain structures [77], so that novel targets in the pain neuromatrix could be stimulated.

5.3 What is the optimum magnitude of the applied electric current?

The effects of electric stimulation of the brain have long been studied in animal models [79, 80]. When applied to the brain, the current is thought to alter underlying neuronal excitability but is also thought to affect functionally connected distant cortical and sub-cortical regions. However many animal studies apply direct current stimulation onto the cortical area (DCS). Therefore the current reaching the cortex is typically much greater than with transcranial application. The magnitude of electric current may be critical for the observed effects so the two methodologies could differ substantially. Similarly the trans-cutaneous application of electric currents to nerves is also emerging as a useful non-invasive intervention, and again the existing animal and human studies are often based on observations from invasive methods.

tDCS and tACS studies typically apply low currents (typically 1–3 mA) with 1.5–2 mA being the most usual stimulation levels. Recent studies have experimented with the use of higher currents (up to 4 mA) [81]. Studies have varied substantially in the protocols used, but all would lead to charge densities that would be far lower than that required to elicit an action potential. The charge density used in a study varies dependent on the size of the electrodes used, and is calculated by the size of the electrical current applied divided by the electrode area. The duration of the applied electrical stimulation has also been variable across studies but is typically within the range of 10–30 minutes. To enhance intervention comparisons studies could compare the total charge administered over stimulation period, so taking into account the duration electrical stimulation is applied in the intervention period.

Future work exploring the appropriate current, as well as how this can be adjusted for different individuals is essential. It already known that lower currents are sufficient to lead to membrane polarization and have potential therapeutic benefits. Indeed the lower stimulation levels applied to primary motor cortex were in fact more effective in increasing motor cortical excitability [82], and may avoid the problematic finding of non-linear tDCS effects that have recently been reported when increasing current, with a reversal of effects observed in the mid-range of applied current (2 mA) [83]. This observation has been paralleled in animal models but pharmacological studies are required to discern the effect of the current on specific ion channels. Since it has been reported that there is non-linear effect in the stimulation magnitude, individual differences in cortical excitability; determined by differences in motor evoked potentials when primary motor cortex is the target; could become critical for appropriately setting therapeutic dose.

A further tDCS effect that has not undergone much investigation and yet is important for implementation in a patient population is the duration of any tDCS therapeutic effects, and the impact of protocols involving repetitive stimulation is applied. Recent research has explored the short and long stimulation durations and compared these with those where short duration protocols are repeated with intervals. There is some evidence that repeated stimulation is more efficacious than continual longer duration stimulation protocols [84].

5.4 Interaction with individual patient characteristics

There are multiple parameters that can be altered in the administration of tDCS stimulation [48]. There will also be alterations of the effect of tDCS due to differing characteristics of the patient. There will be environmental factors that will impact on tDCS effects that could include the patient's current cognitive state and fatigue levels. Increasingly studies have explored the interaction between tDCS and pharmacological interventions, but it must also be considered that other medications taken by the participant could impact on the effect of neurostimulation. Many of the conditions that tDCS has been proposed to treat would mean that the patient would be taking medication [85]. This is particularly critical when considering the use of tDCS for pain relief, as chronic pain is a frequent comorbidity. Hormonal influences have been suggested to impact both on the perception of pain but also on the effects of tDCS. The effect of the interaction of tDCS with estrogen has only recently been explored [86]. This is particularly important when considering pain interventions as many conditions associated with chronic pain have a higher prevalence in women than men.

5.5 Mechanisms of tDCS

The effect of tDCS has been shown to be polarity-dependent [87]. Application of the anodal electrode (a-tDCS) over the target area increases neuronal excitability whereas a cathodal electrode (c-tDCS) decreases neuronal excitability [70, 88]. The underlying mechanisms of tDCS effects are unclear but tDCS is thought to alter neuronal membrane potential and so impact on the action potential threshold [89]. These studies suggest that anodal stimulation induced neuronal excitability results from neuronal membrane subthreshold depolarization and cathodal inhibitory effects are produced by membrane hyperpolarization. It was originally proposed that the polarization was from the somatic membrane where there is a higher density of sodium channels. Following from this, the short term effect of tDCS have been suggested to be related to increasing permeability to sodium. Additionally the neuronal excitability that occurs during anodal tDCS can be removed by pharmacologically inhibiting calcium channels and voltage-dependent sodium channels [90].

Human spectroscopy studies have demonstrated that anodal tDCS causes a local gamma aminobutyric acid (GABA) reduction [91] whereas cathodal stimulation leads to decreased glutamatergic neuronal activity. Currently the suggested mechanism of tDCS is thought to include presynaptic modulation of neurons, with the stimulation effects related to synaptic inputs rather than solely action potential generation [92, 93]. Evidence from animal studies of DCS also suggests presynaptic effects, with cathodal stimulation reducing the probability of glutamate release and anodal stimulation increasing glutamate release probability.

To explain the longer term effects of tDCS, anodal tDCS had been initially assumed to induce long term potentiation (LTP)-like effects whereas cathodal tDCS thought to induce long term depression (LDP)-like effects. However this is now thought to be overly simplistic. Some of the variability in effects of anodal and cathodal stimulation has been explained by mechanisms of homeostatic plasticity [94] formalized in the Bienenstock-Cooper-Munro (BCM) rule of bidirectional synaptic plasticity [95]. These mechanisms are proposed to occur within neural networks to prevent hyperactivity or hypoactivity [95].

Importantly recently it has also been highlighted that polarization of the cell membrane must be dependent on the orientation of the neuron to the extracellular current vector [96]. Further evidence of the importance of axonal orientation has been provided by animal studies with evidence from rat hippocampus suggests that effects of electrical current vary dependent on the orientation of axons [97]. The significance of axonal orientation in the effects of DCS could have wider implications as to how develop tDCS methods. Diffusion magnetic resonance imaging (dMRI) enables an assessment of the structural connectivity and integrity of tracts. It has been suggested that tractography achieved from dMRI may be beneficial for optimal electrode positioning in clinical instances where there has been disruption in fibre tracts due to disease [98] or that dMRI may aid understanding of the effects of neuromodulation at a cellular level [99]. Imaging techniques may also offer a means of individualizing interventions, but they would have the disadvantage of a substantial cost increase for an otherwise cheap intervention.

5.6 tACS

Transcranial alternating current (tACS) of the primary motor cortex (M1) has been shown in the past to be effective in modulating sensory thresholds for tactile sensation and visual phenomena [100] and offers potential for pain modulation [101]. tACS involves weak alternating currents being applied through the skull via electrodes on the scalp with montages similar to those used with tDCS. tACS can be applied in a wide frequency range, with the effect of each frequency range still to be explored. There is evidence of gamma and alpha oscillations being associated with pain processing and perception. Despite its potential only a limited number of studies have used tACS although alpha range stimulation has been found beneficial for pain relief [102]. Studies combining tACS with fMRI, neurophysiology or QST may help address the optimum tACS frequency for pain relief. The mechanistic effects of tACS are less well understood than tDCS and interestingly there has been the suggestion that tACS effects could be a result of stimulation of peripheral nerves trans-cutaneously rather than effects on cortical neurons [103].

5.7 Less explored effects of electric currents and future research avenues

Imposed electric fields may have a wider biological effects. For instance tDCS could influence glia [89, 104]. Future work should consider these largely unexplored effects so as to provide a more comprehensive mechanistic basis for weak

electric currents dependent on targeted pain processing region. Further some consequences of weak electric currents are not widely monitored. Recent studies have begun to explore the possible consequences of tDCS on immune responses, which is particularly relevant when considering tDCS and ta-VNS for analgesia. However, thus far this has been in animal models [105, 106]. Imaging techniques such as proton magnetic resonance spectroscopy (H-MRS) could provide a useful methodology for monitoring changes in metabolites in response to patient tDCS or ta-VNS interventions. For instance, choline and myo-inositol are thought to be altered in chronic pain patients and are associated with neuroinflammation [21].

6. Conclusion

Pain is a complex sensation associated with the activity of multiple cortical and sub-cortical regions in the brain. The overall pain percept must result from the interplay between multiple ascending pathways that convey nociceptive input from the peripheral with descending pathways that act to modulate nociceptive input. The mechanisms for the formation of chronic pain are uncertain; though it is known that there are both peripheral, spinal cord and central mechanisms underlying the formation of chronic pain. Non-invasive neuromodulation through tDCS presents a particularly interesting treatment intervention for pain as recent evidence also suggests that its mechanism of action is not only the modulation of neuronal activity but that the technique also influences the neuro-immune response. However, for appropriate translation of tDCS to a clinical setting there remains the need for research for both increased mechanistic understanding as well as studies how the level of electric stimulation applied can be accurately targeted and tailored to individuals and different disease groups.

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