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Review

Transcranial Electrical Stimulation in Migraine – How Does It Work and What Can We Learn from It?

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Abstract

Although being one of the most common neurological disorders, migraine is commonly misunderstood and misdiagnosed. Current treatments rely on pharmacological approaches, which have been shown not to be effective for all, and so alternative, non-invasive treatments are being sought. Transcranial stimulation could be a possible treatment for migraine. Transcranial electrical stimulation generally involves applying a current to the cortex via the scalp. Whilst this has previously been mostly done in clinical settings, the advance of technology means that devices intended for use in the home are becoming more readily available. However, one of the major drawbacks is that we are not sure about the mode of action of transcranial electrical neurostimulation specifically in the case of migraine. The purpose of this review is to consolidate our current understanding of how these methods are thought to work in the case of migraine, considering not only their effectiveness in attempting to treat migraine, but also as a tool to understand migraine as a disorder.

Keywords

tDCS; tACS; hf-tRNS; anodal; cathodal; excitation; inhibition, ion channels; GABA

1. Introduction

Migraine is one of the most common neurological disorders, affecting around 10% of the population [1], and posing a large economic burden [2]. Around half of those experiencing migraine don't seek diagnosis from medical professional [3, 4], and when they do, migraine is commonly misdiagnosed [5]. Less than half of those with chronic migraine were satisfied with their acute treatment [6], and in recent studies on prophylactic medication only around 50% were somewhat or very satisfied [7]. Even those with chronic migraine, classed as more than 15 attacks per month, show low adherence (using as prescribed) to prophylactic (preventative) treatment, less than 30% at 6 months follow-up [8]. Importantly, those with chronic migraine also show low persistence (continuing to take the medication) at around 25% at 6 months [9]. Modern medications such as eptinezumab show promising results in clinical trials for those with chronic migraine [10]. However, use of medication can be a difficult decision for women of childbearing age, who may be one of the most likely groups to experience migraine [11], as there are concerns about taking medication for migraines when planning a family [12].

As an alternative to medication, or to supplement medication, some people have tried behavioural therapies for migraine, for example more recently using apps, but there are barriers to the effectiveness of these methods in terms of time commitment, and how easy the technology is to use [13]. It has been suggested that the efficacy of behavioural treatments is such that benefits are really seen in conjunction with medication, rather than as a stand-alone therapy [14], which would not solve the problem of those who cannot tolerate medication. Therefore, there is a need for alternatives that are more effective than behavioural therapy and can be used by those who are unable to take medication, or for whom the medication does not work. One possibility could be transcranial electrical neurostimulation (tES), however, it is important to understand how this might work in the case of migraine specifically, for example to obtain the correct stimulation protocols and advise potential users appropriately.

2. What We Understand About Migraine

It is unclear what might trigger attacks, and how to prevent their initiation, which is crucial for developing effective preventative treatments. Migraine attacks are associated with a phenomenon called "cortical spreading (depolarisation and) depression", which is a spreading wavefront of strong cortical activity (depolarisation), followed by a cortical "silent period" of reduced activity (depression; for a review, see [15]). Although the role of CSD in migraine is not universally accepted, and does not account for several important clinical features of migraine (e.g. [16]), there is fMRI evidence of a spreading wavefront of strong activity during the migraine aura [17]. It has been suggested that the migraine cortex is susceptible to this phenomenon as there is an imbalance between excitation and inhibition [18].

One suggestion is that the migraine cortex is hyperexcitable [19]. There is evidence for this as in between migraine attacks, those with migraine show differences in performance and brain activity from the sensory areas of the cortex. Typically, it is easier to elicit neural activity in those with migraine compared to controls - using transcranial magnetic stimulation (TMS), Aurora et al., [20] demonstrated a lower phosphene threshold in the migraine compared to the control group. Additionally, visual evoked potentials (VEPs) recorded using EEG are also greater in those with migraine [21]. There are also increased fMRI BOLD responses in those with migraine in response to

striped stimuli [22]. Behaviourally, it has also been shown that those with migraine are especially sensitive to flickering stimuli [23], and it has been reported that visual stimuli can trigger migraine [24]. Taken together, this research showing increased responses to incoming sensory stimuli supports the idea that the cortex might be hyperexcitable in migraine [19].

However, not all research seems to support this suggestion. For example, VEP amplitudes were found to be lower in combined migraine group compared to controls [25]. Additionally, contrast thresholds were elevated in migraine, showing that they were less sensitive to very faint stimuli [26]. Therefore, it has been suggested that there is a lack of inhibition to stimuli, resulting from a reduced initial response level in those with migraine [27]. The suggestion here is that those with migraine have overall lower levels of brain activity, then over-react in response to incoming stimuli to compensate. The idea of reduced inhibition has some support, those with migraine show poorer performance on tasks that depend on inhibitory processes, for example orientation discrimination [28]. Habituation can be thought of as a diminished response to repetitive stimuli, and several studies have shown there to be a lack of habituation to repetitive stimuli in those with migraine (e.g. [21, 29]), although this is not always replicated (e.g. [30]). However, there are longer-lasting motion after-effects in those with migraine [31, 32], which is suggests that inhibitory processing is not impaired.

The majority of research seems to point in the direction of an imbalance between excitatory and inhibitory processes in migraine, but this is not yet fully understood. There have also been some studies into the neurotransmitters involved in migraine. GABA is a key inhibitory neurotransmitter. As a lack of inhibition has been suggested in the case of migraine, GABA agonists have been used to see if they can redress any inhibitory imbalance, with some promising results in experimental settings: GABA agonists normalised visual performance in line with controls [33], and similarly GABA agonists normalised the response to transcranial magnetic stimulation (TMS) in migraine [34]. However, a Cochrane review of the literature showed that GABA agonists don't seem to help prevent migraine [35].

It has been suggested that hyperexcitability of the cortex could be due to glutamate in the case of migraine [36]. Glutamate is thought to have a role in the development of the CSD, as medication that blocks this prevents CSD development [37]. However, glutamate levels also have a role in the pain pathways, as glutamate levels increase in the thalamus during the experience of pain [38]. Studies have demonstrated increased levels of glutamate in migraine in the occipital cortex [39]. Other work has found an increased glutamate/glutamine ratio in the visual areas in migraine, suggesting that the level of glutamate *per se* is not the issue, but the relationship between the levels of glutamate in the neurons to glutamine in the astrocytes that is key [40]. However, in the case of children with migraine, *lower* glutamate levels were seen in the visual cortex [41]. It seems most likely that there is a complex imbalance of excitatory and inhibitory processes that contribute to migraine, and there is evidence that these change with the development of the disorder [41].

As mentioned previously, the role of CSD in the pathogenesis of migraine is still debated. One of the issues with this explanation is that CSD does not account for the pain of the migraine attack. The vascular system has been implicated as a source of pain in migraine the idea being that vasodilation of the extracranial arteries leads to increased pain [42]. Stimulation of the trigeminal nerve, which is implicated in migraine, leads to release of calcitonin gene-related peptide (CGRP) [43]. In addition, CGRP is a vasodilator of the temporal arteries and levels are elevated in those with migraine [44]. In addition, the abortive medication triptan reduces CGRP levels in the extracranial arteries [45].

Therefore, there is a link between trigeminal nerve stimulation, CGRP release, and the pain of migraine, which some argue to be due to vasodilation. However, CGRP antagonists used as migraine treatment do not affect cerebral blood flow [46]. Additionally, artificial vasodilation of the cranial arteries achieved with vasoactive intestinal peptide does not elicit headache pain in those with migraine [47]. Moreover, blood flow during migraine attacks induced using nitroglycerine was not increased compared to baseline [48]. Therefore, it is likely that there is a role of the vascular system in migraine in terms of the experienced pain, but the vascular system is neither necessary nor sufficient to account for the migraine attack as a whole.

As well as the cortex, widespread areas of the brain have also been shown to be involved in migraine pathogenesis, in particular implicating their role in pain modulation. There is evidence of reduced brainstem function to modulate descending pain pathways [49], although it should be noted that there was no difference in the subjectively reported pain between migraine and control groups in this study. Fumal et al., [50] showed the hypometabolism in several areas of the brain involved with the processing of pain, including the thalamus, cerebellum, insular and parietal areas, and that these areas increased in metabolism with the withdrawal of long-term analgesic medication. However, there have been arguments made against this explanation that these patients were those with medication overuse headache specifically, there are many with episodic migraine who do not develop this condition, as well as the possibility of placebo effect from the withdrawal of the medication [51].

It has been suggested that migraine is characterised by differences in the pain pathways. The dorsolateral prefrontal cortex is thought to have a role in modulating the experience of pain, specifically there is lower activation with more unpleasant stimuli [52]. In addition, activity in the left dorsolateral prefrontal cortex has a negative relationship with activity in the thalamus, whereas the right dorsolateral prefrontal cortex relates to activity in the insular. This is important as both these areas are associated with the experience of pain, leading the authors to conclude that the dorsolateral prefrontal cortex may have a role in moderating the experience of pain [52]. In the case of migraine, there is reduced grey matter volume and reduced functional connectivity in the frontal cortex in those with migraine without aura compared to controls [53]. TMS of the sensorimotor areas was found to increase pain sensitivity, whilst TMS of the medial frontal cortex was shown to reduce pain sensitivity in migraine [54]. Stimulation using TMS of the dorsolateral prefrontal cortex has been shown to reduce pain sensitivity [55]. This is relevant to tES stimulation in migraine as interventions designed to increase activity over frontal areas are hypothesised to aid the modulation of the pain pathways.

As migraine is not yet fully understood as a disorder, it is difficult to precisely predict what effects neurostimulation will have on the migraine cortex. However, studies into the effectiveness of neurostimulation as a possible treatment for migraine are becoming more numerous as people seek alternative therapies. As neurostimulation techniques can demonstrate causality, these may also help develop our theoretical understanding of migraine.

The following is a narrative review specifically of transcranial electrical stimulation in migraine. Articles were found using the following searching engines and databases: Web of Science, Google Scholar, PubMed, using the following search terms: “migraine”, “migraine aura”, “migraine without aura”, “classical migraine”, “common migraine”, “neurostimulation”, “transcranial neurostimulation”, “transcranial electrical stimulation”, “transcranial alternating current stimulation”, “transcranial direct current stimulation” “anodal stimulation”, “cathodal stimulation”.

In addition, articles citing other relevant articles were used. As the narrative review is focussed on transcranial electrical stimulation, articles exclusively covering other forms of stimulation e.g. TMS, intercranial stimulation, were excluded. Additionally, work focussed on other headache disorders distinct from migraine, such as other primary headaches (e.g. cluster headache) and also the secondary headaches, were also excluded.

3. Transcranial Electrical Stimulation in Migraine

Low intensity transcranial electrical neurostimulation is thought to be quite safe in general, if appropriate procedures are adhered to [56]. As there is an intention for the devices to be used at home, their use should be accompanied with appropriate training and supervision, and the possibility that neurostimulation should be regulated has been raised [57-59].

A recent review suggested that 4 weeks are needed to see benefits of neurostimulation in migraine [60], suggesting effects are subtle and need time to accumulate. In studies of perceptual learning, it has been shown that a concurrent task boosts the effect of neurostimulation [61] and so it is possible that a combined task with neurostimulation protocol might amplify any benefits in migraine. However, it appears there is limited research combining potentially therapeutic tasks with neurostimulation in the case of migraine.

3.1 Transcranial Direct Current Stimulation (tDCS)

3.1.1. Mechanism of Action

There are several studies investigating the effects of tDCS in migraine. However, there considerable variation between the types of participants included in the studies, whether chronic or episodic migraine, with or without aura, and also variation in the stimulation protocols. The studies reported in this section are summarised in Table 1 for ease of referral.

Anodal tDCS is thought to be excitatory, whilst cathodal tDCS is thought to be inhibitory [62]. It has been suggested this is due to direct effects on the overall polarity of the cell membrane, increasing the probability of responses or decreasing them, respectively. There is also evidence of tDCS affecting neurotransmitters like GABA, specifically, anodal tDCS increases connectivity and decreases GABA levels in motor cortex [63-66]. However, the amount of change of these is not correlated, suggesting possibly different underlying mechanisms for the two [66]. There are also effects reported on glutamate and glutamine - anodal stimulation increases Glx at the stimulation site, but not in the contralateral hemisphere [67]. Conversely, cathodal tDCS decreases glutamate levels [63].

One of the arguments is that the migraine cortex is hyperexcitable [19], the logic for several studies is to reduce hyperexcitation by applying inhibitory, cathodal stimulation, specifically over sensory areas.

However, other authors take a different approach. DaSilva et al., [68] applied anodal stimulation to those with chronic migraine. It has been suggested that those with migraine are sensitised to pain (e.g. [69]), therefore anodal stimulation, thought to be excitatory, was applied to the more anterior areas to provide analgesic effects by moderating the pain pathways.

3.1.2 Clinical Outcomes

Studies testing the idea of reducing sensory cortical excitability have used inhibitory, cathodal stimulation. Antal et al., [70] applied cathodal stimulation to early visual areas 3 times per week for a duration of 6 weeks. Compared to the sham group, the intensity of pain was reduced, but none of the other outcome variables were different compared to sham. Similarly, Rocha et al., [71] applied cathodal tDCS over occipital areas. Stimulation consisted of 12 sessions, and participants kept a headache diary to monitor their symptoms. There was a reported decrease in number of attacks, and a decrease in the use of acute medication in the stimulation group, but not the sham group. There was no difference found in the phosphene threshold after neurostimulation. This is important as the phosphene threshold is an index of excitability, and those with migraine tend to have lowered phosphene thresholds (e.g. [72]). Wickmann et al., [73] used repetitive cathodal tDCS over visual cortex to decrease cortical excitability as measured by TMS in menstrual migraine. The overall number of migraine attacks showed a tendency to reduce, but this was not statistically significant when compared to the sham group. Ahdab et al., [74] also applied cathodal tDCS over occipital cortex. Stimulation was 2 mA for 20 minutes and there were three sessions on consecutive days. Participants reported reduced migraine duration, pain intensity, and reduced acute medication use. The benefits were reported to last for over 2 weeks. Overall, this shows that there may be some evidence of benefits of cathodal stimulation over occipital areas in migraine, in terms of reducing number and/or intensity of attacks, but this may depend on the intensity of the stimulation and the number of sessions, which varies between studies.

Other authors tested the idea that excitatory anodal frontal stimulation will enhance the pain modulation pathways. DaSilva et al.,[69] showed that after anodal stimulation over the motor cortex on alternate weekdays for a period of 10 weeks, participants reported decreased pain intensity compared to baseline. Similarly, Auvichayapat et al., [75] applied anodal stimulation over the motor cortex for 20 days, and participants were followed up for 12 weeks. There was an improvement in pain intensity, reduced attack frequency and reduced use of acute medication to abort attacks. In a retrospective study including several different headache types including migraine, Pinchuck et al., [76] showed some benefit in reducing number of attacks with migraine, with anodal stimulation over frontal areas and the cathode over the mastoid (bones behind the ear). Przeklasa-Muszyńska et al., [77] also found a reduced use of acute medication to abort attacks after anodal stimulation over motor cortex, however it is important to note there was no sham stimulation condition in this study. This is not limited to motor cortex - Andrade et al., [78] applied 12 sessions of anodal tDCS to the dorsolateral prefrontal cortex (DLPFC) and motor cortex. Stimulation of either region reduced pain intensity compared to sham control, however more adverse effects were reported after stimulation to motor cortex. Some authors have also combined anodal tDCS over motor cortex with trans-spinal direct current stimulation and shown a reduction in headache frequency, although it must be noted that this was a feasibility study with only 3 individuals with chronic migraine, and the report does not include a sham condition [79].

Curiously, there seems to be a pattern emerging that both cathodal occipital, and anodal frontal/motor tDCS seems to be of benefit in migraine. More recently, Mansour et al., [80] showed a benefit of both anodal stimulation over prefrontal areas, and cathodal occipital stimulation, in terms of reduced number of days with migraine days in those with medication overuse migraine. Moreover, effects of cathodal occipital stimulation lasted longest at follow-up. It is possible that

these two theoretical mechanisms can co-exist, as they are not mutually exclusive – there could be combined actions of reducing excessive occipital activity (cathodal occipital) and/or increasing excitation in the areas that are responsible for the management of pain (anodal frontal/motor).

However, other authors seem to dispute the idea that cathodal occipital or anodal frontal/motor could be the correct configuration for benefits in migraine. Viganò et al., [81] applied *anodal* stimulation over the visual cortex. Coppola et al., [21] suggested that the lack of habituation could be due to reduced initial levels of excitation. Viganò et al., [81] showed tDCS increased habituation in both migraine and control groups as shown by visual evoked potentials (VEPs), as well as participant reported outcomes including reduced attack frequency and duration, and reduced use of acute medication to abort attacks. Importantly, this study did not use sham control, but did have a control group of healthy volunteers who also underwent stimulation. The drawback with this design is that there is the possibility that self-reported measures might be influenced by placebo effects, as all participants will be aware of the stimulation. However, the visual evoked potentials (VEPs) should be objective measures and so not prone to placebo effects. Critically however, as tDCS affected habituation in both groups this does not represent an effect specific for migraine.

Conversely, Ramini et al., [82] used *cathodal* tDCS over somatosensory and motor areas, for 3 sessions per week over 5 weeks, showing benefit in migraine frequency, duration and intensity, both straight after testing and also at follow-up at one year. Dalla Volta et al., [83] demonstrated in a large study with 45 participants with chronic migraine, that frontal *cathodal* tDCS resulted in improvement over all measures compared to sham, including fewer migraine attacks, headache days, shorter duration, and less intense attacks. Importantly, the exact placement of the frontal stimulation was located over the "cold patch" which has been identified as characteristic of chronic migraine – one area of the forehead seems to be lower temperature in comparison to the rest [84]. These results are difficult to reconcile with our theoretical understanding of mechanisms of migraine. It seems to be the case that the arguments for analgesic effects of anodal neurostimulation over frontal areas may not be correct, as cathodal stimulation over these areas also seems to show benefits. As the proposed mechanism is an analgesic effect, it is not possible to devise a test to measure this objectively, as the very experience of pain is by definition subjective.

To further complicate the issue, other authors have shown evidence that neither anodal, nor cathodal tDCS shows any benefit for chronic migraine due to medication overuse compared to sham, and this study was a large randomised controlled trial [85]. The primary outcome in this study was a 50% reduction in migraine days at 12-month follow-up. As the stimulation was a 5 consecutive day period, it seems this is rather short to be seeing effects at 3 months and onwards. It is unclear how long the effects of tDCS last for, and this is likely to depend on stimulus intensity, duration and the number of sessions, but in many studies washout periods are considerably shorter than 3 months, for example in tinnitus, suitable washout periods were defined as 2 weeks [86]. It should be noted that other authors finding effects compared to sham at 12 weeks had many more sessions of tDCS, for example 20 sessions [75] and 12 sessions [78].

This presents a confusing set of results for the mechanism of tDCS in migraine. Cathodal occipital stimulation was suggested to reduce excessive visual responses, however there are also studies showing that anodal occipital stimulation is beneficial in migraine. Anodal frontal/motor tDCS was suggested to be beneficial in migraine due to analgesic effects from stimulating the pain modulation areas, however benefits have also been shown for cathodal frontal/motor stimulation. It could be that our understanding of migraine pathophysiology as "excitatory" or "inhibitory" is too simplistic.

Importantly, effects of anodal stimulation are reduced by blocking Na^+ channels, and the duration of effects of tDCS (both anodal or cathodal) after applying an NMDA antagonist [87]. This is important as the Na^+ channels have been implicated in one type of familial hemiplegic migraine [88], and modelling work has demonstrated the theoretical importance of ion transfer in the balance between excitation and inhibition in the migraine brain, including Na^+ [89]. However, another type of familial hemiplegic migraine is associated with disruption to Ca^{2+} [90]. Therefore, the neurochemical balance is not simple, and there are additional candidates such as potassium ions [91], and calcium channels [92]. It must be noted that much of the work has focused on familial hemiplegic migraine, a rare and genetic form of migraine aura, of which there are animal models. However, it could well be the case that similar processes underpin episodic migraine, but the ion(s) involved in episodic migraine have yet to be demonstrated conclusively.

Table 1 shows the details of the studies using tDCS in those with migraine.

Study	Anodal/ Cathodal	Location of Stimulation	No. Sessions	Duration of treatment	Amp	Patient Population	Number of participants	Study type	Results
Antal et al., (2011) [70]	Cathodal	Early Visual areas	3 per week	6 Weeks	0.4 mA	Migraine	30 (dropout 4)	RCT	Intensity of pain reduced
Rocha et al., (2015) [71]	Cathodal	Occipital areas	12 × 20 mins	4 weeks	2 mA	Migraine with/without Aura	19	RCT	Decrease no. Attacks Decrease use of acute medication
Ahdab et al., (2019) [74]	Cathodal	Occipital Cortex	3 on consecutive days	3 days	2 mA	Episodic Migraine	53 (dropout 11)	RCT	Decreased migraine duration and pain intensity. Decreased use of acute medication Effects lasted approx. 2 weeks
Wickmann et al., (2015) [73]	Cathodal	Visual Cortex	5 × 20 min	Once a month over 3 menstrual cycles	2 mA	Menstrual Migraine	20 (dropout 4)	Proof of concept	Decreased attack frequency
DaSilva et al., (2012) [68]	Anodal	Motor cortex	10 × 20 mins	4 weeks	2 mA	Chronic Migraine	13	RCT	Decreased pain intensity and duration.
Auvichayapat et al., (2012) [75]	Anodal	Motor Cortex	20 mins daily	20 days	1 mA	Episodic Migraine	42 (dropout 5)	RCT	Decreased pain intensity and attack frequency. Decrease use of acute medication

Przeklasa-Muszyńska et al., (2017) [77]	Anodal	Motor Cortex	10 × 20 mins	30 days (2-3 × weekly)	2 mA	Migraine with/without Aura	50	Proof of concept	Decreased use of acute medication
Andrade et al., (2017) [78]	Anodal	DLPFC and Motor Cortex	12 × 20 mins	4 weeks	2 mA	Refractory Chronic Migraine	13	RCT	Decreased pain intensity. Some adverse effects reported after stimulation of Motor Cortex
Alhassani et al., (2017) [79]	Anodal	Left Primary Motor cortex and 10th Thoratic Vertebrae (T10)	40 mins a day	5 days	1 mA	Chronic Migraine	9	Proof of concept	Decreased frequency of headaches.
Pinchuck et al., (2013) [76]	Anodal Cathodal	Frontal pole of subdominant hemisphere. Ipsilateral mastoid process	5-9 × 30-45 mins	1 session every 4-7 days	70-150 µA	Migraine without Aura	134	Proof of concept	Decreased attack frequency and intensity
Mansour et al., (2020) [80]	Anodal Cathodal	Prefrontal Cortex Occipital cortex	3 × 20 mins	3 consecutive days	2 mA	Migraine Medication Overuse Headache	18	RCT	Decreased migraine frequency and severity. Only cathodal showed improvements lasting more than 2 weeks
Viganò et al., (2013) [81]	Anodal	Visual Cortex	2 per week	8 weeks	1 mA	Migraine without Aura	24	Proof of concept	Decreased attack duration and frequency. Decrease use of acute medication

Pohl et al., (2021) [109]	Anodal	Visual Cortex	daily	5 months	1 mA	Migraine with and without aura	23	RCT	Decreased number of migraine days, but only in months 2, 3 and 4 compared to baseline
Dalla Volta et al., (2020) [83]	Cathodal	Prefrontal cortex over the 'cold patch' (determined by thermographic examination)	5 × 15 mins	Once a day for 5 days	1.5 mA	Chronic Migraine	45	RCT	Decreased frequency, duration, and pain intensity of attacks.
Ramini et al., (2020) [82]	Cathodal	Motor Cortex and Sensory Cortex	3 × 20 mins per weeks	10 weeks	1000 µA	Migraine (episodic, chronic, with/without aura)	45	RCT	Decreased frequency, duration and intensity of attacks

3.2 Transcranial Alternating Current Stimulation (tACS)

tACS uses an alternating current, changing the polarity of the electrodes from anode to cathode and vice versa. The frequency refers to the rate of the switch in polarity, and this can be set to any value. tACS is thought to work by entraining oscillations. This can be achieved in more than one way; one possibility is that the stimulation results in phase resetting of the ongoing oscillations. Alternatively, tACS could cause the membrane potential of the cells to change in an oscillatory way, resulting in fluctuating probability of firing, and therefore increases and decreases in overall activity [93]. There can be resonance-like effects of tACS, [94] showed that applying tACS at the frequency of the alpha band for each individual resulted in maximally increased alpha power.

Different frequencies of tACS are thought to affect different cell populations. 40 Hz tACS seems to affect interneurons, whereas lower frequencies affect the pyramidal cells [95]. Additionally, tACS can also affect neurotransmitters – 75 Hz tACS reduced GABA levels inferred through TMS [96].

There are few tACS studies on migraine to date, this can be seen in Table 2. Antal et al., [97] applied 140 Hz tACS at 0.4 mA for 15 minutes over the motor cortex as an acute treatment for migraine, with some limited success. Compared to sham, there was reduced pain severity when tACS was applied 2-4 hours after the onset of the attack. tACS made no difference to whether participants took acute medication. tACS in this experiment was aimed at the acute treatment of migraine. As effects of neurostimulation are fairly small, it may be the case that they do not have sufficient power to be an effective acute treatment.

Table 2 shows the details of the studies using tACS in those with migraine.

Study	Freq	Location of Stimulation	No. Sessions	Duration of treatment	Amp	Patient Population	Number of participants	Study type	Results
Antal et al., (2020) [97]	140 Hz	Motor	Acute treatment	15 mins	0.4 mA	Migraine with and without aura	25	RCT	Pain-free in 2 hours for 14/38 attacks for tACS, 0/23 for sham stimulation. Reduced pain severity after tACS compared to sham stimulation

3.3 Transcranial Random Noise Stimulation (tRNS)

tACS is the application of an alternating current with variable frequencies. Frequencies are randomly chosen, usually in a specified range. These are broadly categorised into two types, low-frequency tRNS (under 100 Hz), and high-frequency tRNS (over 100 Hz) (for a review, see [98]). Some authors suggest the most likely action is due to increased cortical facilitation due to repeatedly opening Na^+ channels [99]. tRNS has also been suggested to work through the process of stochastic resonance [100, 101]. Stochastic resonance is when a sub-threshold signal has a small amount of noise added to it, which apparently paradoxically increases, rather than decreases performance. If a large amount of noise is added, all that is perceived is the noise, as the signal is "swamped". However, if the noise is just strong enough to boost the signal over the detection threshold, but not overpower it, then this results in an apparently paradoxical improvement in performance. The low levels of alternating current at random frequencies are thought to provide this small amount of noise and therefore have a facilitatory effect [98].

There is evidence of a facilitatory effect of hf-tRNS specifically - hf-tRNS over motor cortex, 100-640 Hz for 10 minutes at 1 mA has been shown to increase cortical excitability, and effects last for around 1 hour after stimulation [102]. Herpich et al., [103] applied hf-tRNS (101-640 Hz) for 20 minutes at 1 mA over V1, and reported reduced phosphene threshold, an effect that lasted for around 1 hour afterwards. There was no such reduction in phosphene thresholds from the sham stimulation, and no difference from anodal tDCS either.

tRNS can also act on GABA - GABA levels in mice reduced after 0.3 mA for 20 mins tRNS over prefrontal cortex for 9 sessions over 5 weeks [104]. It is also worth noting that these authors also tested 100× higher stimulation levels than would normally be used in humans and did not see any adverse effects [104]. However, the impact on GABA is not clear, in humans, a single session of hf-tRNS (100-640 Hz) for 10 minutes does not affect processes thought to rely on GABA [105]. However, this was assessed using indirect behavioural methods (grating orientation discrimination), rather than direct measures of GABA levels. Terney et al., [102] also found no effect on behavioural methods thought to rely on GABA. The second important thing to note is that both these studies there were limited number of tRNS sessions, Saito et al., [105] used only a single session of tACS, and Terney et al., [102] had two sessions. Whereas the effect of GABA in animal models was seen after 9 tACS sessions [104].

There are very few studies using tRNS in migraine. O'Hare et al., [106] applied hf-tRNS to a migraine group when performing a motion perception task. Internal noise estimates were found to be higher in the migraine compared to the control group, and these were reduced in both groups compared to sham. However, the migraine group was now in line with the internal noise estimates of the control baseline, suggesting hf-tRNS might have a normalising effect.

4. Discussion

Transcranial electrical stimulation has in general been suggested for use as a prophylactic (preventative) therapy rather than an acute remedy during the attack itself, unlike TMS. As TMS is thought to directly induce neural firing [107], this has been used in the past for acute treatment, with some success [108]. By contrast, as electrical neurostimulation is thought to affect the membrane potential, rather than driving action potentials directly, this has been used more for

prophylactic treatment. One exception to this is the work by Antal et al., [97] using 140 Hz tACS as an acute treatment, although this did not show much benefit. For tES to be a more practical prophylactic therapy, this needs to be able to be used at home, rather than needing to regularly attend clinic appointments. Developments are currently underway to include the transcranial electrical neurostimulation devices for home use, and this has been done in recent research [97, 109]. However, it should be noted that to date, only the single-pulse transcranial magnetic stimulation (sTMS) device has been approved by the FDA for the treatment of migraine. sTMS is a treatment for acute migraine, rather than intended as a prophylactic. The device consists of a coil electromagnet, and through electromagnetic induction this evokes an electrical current causing the neurons to depolarise. It is thought to disrupt CSD in animal models [110]. In the case of acute migraine treatment, a single or double pulse is administered on attack onset. There is a minimum interval of 15 minutes between pulses. Individuals can administer a total of 16 pulses (or 8 double pulses) in any one day.

It is difficult to directly compare sTMS and tES techniques as they have different intended usage, and different outcome measures. sTMS is self-administered, at home, as needed, to a maximum of 16 pulses per day, whereas the intended usage for tES methods is to continue to use the stimulation regularly as a preventative method, for example daily [109]. A meta-analysis of randomised controlled trials showed that sTMS has been shown to be effective for acute migraine treatment for episodic migraine with aura, but not with chronic migraine, measured in terms of the number of patients pain-free 2 hours after the attack [111]. Only one study using tACS showed this to be effective measured by the number of attacks rendered pain-free 2 hours post stimulation compared to sham [97]. By comparison, tES methods are mostly intended to be used as a prophylactic treatment, and so outcome measures are based on measures such as the number of headache free days, reduction in pain intensity. A recent randomised controlled trial showed there to be a reduction in the number of migraine days per month compared to sham, for example a reduction of -1.7 (+/- 0.5) after anodal tDCS but 0.2 (+/- 0.4) after sham stimulation [109]. In a report of the post marketing pilot programme of sTMS treatment, long-term usage of sTMS was found to also reduce the number of migraine days on average from 15 to 8 at 12 weeks [112].

Neurostimulation using tDCS has shown some benefits for those with migraine. Both occipital cathodal and central-frontal anodal stimulation seems to be of benefit, which is curious as there are distinct predictions about what should happen in those cases. Further, it may be suggested that the anodal stimulation over visual areas may be of more benefit during the initial stages of the migraine attack, perhaps around the time of aura, whereas the frontal anodal stimulation might be important during later stages of a migraine attack, specifically the headache phase. However, this is speculative, particularly as tDCS is generally not applied during the migraine attack itself, but in between attacks. Alternatively, it could be argued that this effect is due to the reliance on self-reports, however these are the most important clinical outcomes in migraine [113]. The use of migraine diaries in many studies to report clinical outcomes such as migraine frequency would arguably be quite a robust method [114], however recent use of a mobile application to monitor headaches has shown relatively low adherence [115]. Additionally, sham-controlled studies mean any effects are difficult to explain as placebo alone. It might worth using an objective measure of performance at the same time to see the effects of the neurostimulation on the migraine cortex in conjunction with the reported clinical outcomes. For example, 2 mA anodal tDCS over occipital cortex has been shown to

have a normalising effect on habituation of visual evoked potentials measured using EEG in those with episodic migraine [116].

One issue with the research overall is that there is considerable variation in neurostimulation protocol. This makes it difficult to draw comparisons between studies and to draw firm conclusions. Decisions around stimulation protocol needs to satisfy conflicting demands, for example the total current density needs to remain low due to safety and ethical issues. Duration of exposure needs to be kept as low as necessary to limit exposure, as well as limiting the risk of participant drop-out. It is interesting to note that Rocha et al., [71] report that all participants who dropped out were in the sham group, rather than the experimental group. There are very few tACS and tRNS studies in migraine from which to draw any conclusions. However, as both the tACS [97] and the tRNS study [106] consisted of a single session of neurostimulation, it would be important to see whether repeated sessions affect clinical outcomes. As it has been suggested that 4 weeks is needed to see any effect [60], stimulation protocols should last this long in future tests.

There is also variation in the types of participants included. Migraine is heterogeneous disorder, with subtypes including migraine with and without aura, migraine related to the menstrual cycle, migraine related to medication overuse, etc. It is possible that there are different underlying pathologies for the subtypes. It is plausible that those experiencing migraine with visual aura might benefit from neurostimulation targeting the visual cortex, whereas other subtypes may not. It would be beneficial to investigate neurostimulation techniques in particular subtypes specifically to further our understanding of migraine pathophysiology.

For some individuals, for example those who are unable or unwilling to take medication, their needs will be to use neurostimulation alone. However, for others, they may be looking to use neurostimulation to complement their current medication usage. Many of the studies excluded participants who were taking medication to prevent migraine (e.g. [70, 71, 73, 75, 80]). There are few studies expressly looking into including the effects of transcranial electrical neurostimulation in conjunction with medication (e.g. [83]). When used in conjunction with topiramate, cathodal tDCS applied over the frontal cortex reduced frequency of attacks, number of days with headache, duration of attacks, pain intensity and the number of painkillers used, compared to control. This suggests that transcranial electrical stimulation can be used in conjunction with medication, although drawing firm conclusions on the basis of limited data is not advisable.

The suggested mode of action for tES is focussed on influencing the neural activity. However, there is evidence that there may be an effect of tES on the vascular system, which is linked to the pain of migraine. Studies using animal models have shown dural and pial artery dilation with bipolar tES [117], as well as increased blood flow with anodal tDCS stimulation [118]. In humans, anodal tDCS over the motor cortex has been shown to increase cerebral blood flow, and conversely cathodal tDCS has been shown to reduce cerebral blood flow, it is thought that the changes in cerebral blood flow with tDCS are through its effect on the neuronal activity, rather than a direct effect on the blood vessels themselves [119]. However, as anodal tDCS results in vasodilation of the vessels of the skin [120], it may well be the case that there is a direct effect separate from cortical effects. Additionally, in humans, tDCS has been shown to affect the ability of the vascular system to dilate the blood vessels, specifically, anodal tDCS reduces the ability to dilate and cathodal increases it [121], therefore there may be an effect of tDCS on cerebral blood flow independent of neuronal activity, however, this is difficult to separate experimentally. Therefore, it may be unwise to draw

conclusions from studies based on transcranial electrical stimulation in relation to the trigeminal-vascular theories of migraine pathogenesis.

Importantly, there are side effects associated with transcranial electrical stimulation. Bikson et al., [122] reviewed the literature showing there to be no evidence of serious adverse effects following transcranial direct current stimulation. This was a summary of over 1,000 participants when studies were combined. Possible side effects included skin irritation, that was reported to resolve after the stimulation was stopped. Nikolin et al., [123] conducted a systematic review of 158 studies including a total of 4130 participants. These studies included healthy populations as well as those with neurological disorders for example, pain, stroke. The adverse effects reported include discomfort, dizziness erythema, fatigue, headache, paraesthesia. The incidence rates of adverse events did not differ between sham and active stimulation. Additionally, there was no evidence of cumulative effects of multiple sessions. One of the most commonly reported side effects is skin irritation, thought to be due to the vasodilatory effect of stimulation on the blood vessels of the skin [120]. However, given the right training and following the standard procedures, the current literature suggests there is minimal risk of serious side effects from transcranial electrical stimulation.

5. Conclusions

Transcranial electrical stimulation has some promising potential in migraine prophylaxis, however, more systematic research is needed to determine the most effective stimulation protocols and the subtype of migraine most likely to benefit. Neurostimulation can also help us understand more about migraine, as it may be argued that there is an imbalance of excitation and inhibition in migraine that could be the source of the issue. It would be beneficial to include more behavioural measures directly testing theoretical predictions of the mechanisms as well as the clinical outcomes.

Author Contributions

LOH and RG contributed to writing and editing the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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