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REVIEW

Efficacy and mode of action of external trigeminal neurostimulation in migraine

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ABSTRACT

Introduction: Available preventive drug treatments for migraine lack complete efficacy and often have unpleasant adverse effects. Hence, their clinical utility and therapeutic adherence are limited. Noninvasive neurostimulation methods applied over various peripheral sites (forehead, mastoid, upper arm, cervical vagus nerve) have raised great interest because of their excellent efficacy/tolerance profile. Among them external trigeminal nerve stimulation (eTNS) was first to obtain FDA approval for migraine therapy.

Areas covered: All clinical trials of eTNS as preventive or acute migraine treatment published in extenso or presented at congresses are reviewed. The paper analyzes neuroimaging and neurophysiological studies on mechanisms of action of eTNS. As many of these studies point toward the anterior cingulate cortex (ACC) as a likely eTNS target, the paper scrutinizes the available literature on the ACC implication in migraine pathophysiology.

Expert commentary: eTNS is a viable alternative to standard pharmacological antimigraine strategies both for prevention and abortive therapy. eTNS could chiefly exert its action by modulating the perigenual ACC, which might also be of interest for treating other disorders like fibromyalgia or depression. It remains to be determined if this might be a common mechanism to other peripheral noninvasive neurostimulation methods.

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1. Introduction

1.1. Pharmacotherapy of migraine

Although cognitive-behavioral therapies can be useful as add-on therapies in some patients, currently, migraine is mostly managed with pharmacological treatments. Acute migraine drugs like analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans [1] are used to interrupt a migraine attack and allow patients to recover normal functioning as soon as possible [2]. Triptans, the agonists of 5-HT1B/D serotonin receptors, are up to now the most effective drugs for severe attacks. They can, however, induce class-specific side effects like chest, face, and limb pain or discomfort that are difficult to tolerate by many patients. Moreover, they are vasoconstrictors and contraindicated in case of comorbid cardio- or cerebrovascular pathology. Migraine patients with frequent attacks or attacks not responding adequately to acute treatments are in need of a preventive antimigraine treatment able to modify the disease course by decreasing attack frequency and intensity [3] so that excessive consumption of acute antimigraine drugs does not lead to headache chronification, i.e. so-called medication overuse headache, which worsens the patients' condition [4].

Effective preventive drugs include beta-blockers without intrinsic sympathetic activity, certain calcium channel blockers like flunarizine or verapamil, sartans, the antiepileptics topiramate and valproate, and possibly amitriptyline [5], as well as nutraceuticals like riboflavin and coenzyme Q10 [6]. Preventive migraine drugs have only partial efficacy with an overall 50–60% success rate and, except for the nutraceuticals, they tend to cause moderate to severe side effects, frequently leading to dissatisfaction and discontinuation by the patients [7–9]. Consequently, 80% of patients are willing to change their current medication for a treatment with similar efficacy but fewer side effects [10]. The therapeutic efficacy of migraine preventives decreases sharply with migraine chronification, which explains why up to 50% of chronic migraine patients discontinue their prophylactic drug treatment after 2 months [11].

1.2. Neurostimulation as an alternative antimigraine treatment

The shortcomings of pharmacological migraine management and technological advances have allowed neurostimulation methods to emerge as credible alternative antimigraine treatments.

Since the 1990s, stimulation of pericranial nerves through percutaneously implanted electrodes was found effective for the treatment of various headaches in various studies [12,13]. Occipital nerve stimulation (ONS) was reported beneficial for chronic migraine in some, but not all, sham-controlled trials, but globally the effect size was modest [14–16]. Combining percutaneous ONS with supraorbital nerve stimulation (SNS) was claimed to have a better effect, but randomized controlled trials are lacking [17]. These neurostimulation methods

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using implanted electrodes may cause various adverse effects chiefly due to local infections, lead displacement or frequent battery replacement, but their major drawback is that they are invasive and indicated only for the most disabled, drug-refractory patients with very frequent and severe migraine attacks [18].

With the advent of noninvasive transcutaneous stimulators neurostimulation therapy became applicable to all migraine patients irrespective of their level of disability or drug-refractoriness [19]. In recent years various transcutaneous stimulation methods were reported to be effective in migraine treatment despite striking differences in targets: bilateral mastoid [20], cervical vagus nerve [21], or skin at the wrist [22]. Several studies of noninvasive neurostimulation in the trigeminal territory showing beneficial effects in various headache types were published as early as 1985 [23–26]; among them, the single-blinded, placebo-controlled trial by Solomon and Guglielmo [23] appears to be the most convincing. Two decades later, technological advances permitted to produce a portable, affordable and user-friendly external trigeminal neurostimulator (eTNS) called Cefaly® (Cefaly Technology sprl, Seraing, Belgium). This device delivers electrical pulses to the forehead branches of the first division of the trigeminal nerve, the ophthalmic nerve, though it can also be applied over the greater occipital nerves via a suboccipital band. The pulses are rectangular biphasic impulses with an electrical mean equal to zero, impulse width of 250 μs, frequency of 60–120 Hz, maximum intensity of 16 mA with an increment from 1 to 16 mA over 14 min. The device has an inbuilt software to record time of use. During the last 4 years several clinical trials have explored the therapeutic effect of eTNS both for the preventive and the acute treatment of migraine. We will review these trials as well as studies aimed at determining the mode of action of eTNS in migraine.

2. Clinical eTNS trials in migraine

For the sake of comprehensiveness, all clinical data of eTNS with this device in migraine that are in the public domain are displayed in Table 1, including manuscripts submitted for publication and abstracts.

2.1. Migraine prevention

Eight studies have addressed the preventive effect eTNS, ranging from an early small pilot trial to a randomized sham-controlled trial [27–34]. In all of them there was a decrease in migraine attack frequency after daily stimulation for time periods between 1 and 4 months, both in episodic and chronic migraine (two open label trials). We will focus briefly on the PREMICE trial [28] where eTNS (n = 34, 250 μs, 60 Hz, 16 mA) was compared to sham stimulation (n = 33, 30 μs, 1 Hz, 1 mA) for a 3-month treatment period. After using the device with the active stimulation protocol 38.1% of patients had $a \geq 50\%$ reduction in monthly migraine days compared to pretreatment baseline, while only 12.1% of patients did so with the sham stimulation. There were no adverse events except for the frontal paresthesias that are known to occur with electrical stimuli. Up to now no trial comparing eTNS with a preventive drug treatment is available. Topiramate, presently one of the most effective drugs, is more efficacious than eTNS in the pooled analysis of placebo-controlled trials reaching a 45.3% of 50% responder rate [29], but it is hampered by unpleasant side effects and low tolerability. For comparison, 1 out of 4 patients taking topiramate abandoned the drug because of intolerable side effects [29], while in a survey of 2313 patients using eTNS 4.3% reported one or more adverse effects, chiefly intolerance to the forehead paresthesias (1.25%) and 2% stopped treatment because of an adverse effect [30]. As a result of the PREMICE trial, the device was the first medical device to get approval from the FDA in 2014 for the preventive treatment of migraine.

2.2. Acute migraine treatment

Since it was marketed, this eTNS device contains a stimulation protocol with a 100 Hz frequency recommended for attack treatment based on a pilot study [27]. In clinical practice many migraineurs have been using this protocol to treat their attacks effectively before evidence-based data became available. In an internet survey, 88.6% of 413 regular users applied the device in 71.8% of attacks, which allowed reducing acute migraine drug use in 42.6% of them [31]. Chou et al. [32,33] were first to scientifically assess efficacy of eTNS for acute migraine treatment in patients stimulated for 1 h in the hospital for an untreated attack that had started ≥3 h before. In the initial open study 77% of patients had ≥50% pain relief at 1 h; in the subsequent multicenter, sham-controlled ACME trial [32,33], 63% of patients reached this end point compared to 31% in the sham arm and 29% were pain-free at 1 h versus 6% with the sham stimulation. This beneficial effect was confirmed in a recent open label study of 48 patients who treated a moderate to severe attack at home for 2 h [34]: 35.4% were pain-free at the end of the stimulation. The 2 h pain-free rates with eTNS are comparable, or even superior, to those reported in recent drug trials of sumatriptan nasal powder (34.3%) [35], the 5-HT1F agonist lasmiditan (28%) [36] or the CGRP receptor antagonist ubrogepant (25.5%) [37]. They are also superior to those found in open studies of noninvasive cervical vagus nerve stimulation (21% and 22.9%) [38,39].

3. Mode of action

Some recent studies have shed some light on possible mechanisms by which eTNS may reduce migraine attack frequency and headache during an attack. eTNS can have an effect on the peripheral and the central nervous system.

Transcutaneous electrical nerve stimulation (TENS), in use since many years to relieve pain [40], is thought to act in part by blocking nociceptive traffic at the segmental level by activating large Aβ afferents according to the gate control theory [41,42]. By analogy, pericranial nerve stimulation could have the same effect by activating somatic afferents from the trigeminal territory or C2 dermatoma that are known to converge with visceral trigeminovascular afferents on spinal trigeminal nucleus second-order nociceptors. This might apply to low intensity–high frequency TENS. Acupuncture-like high intensity–low frequency TENS and high intensity–

Table 1. eTNS with the Cefaly®: efficacy data for migraine prevention and acute treatment.

Study protocol	Number of patients	Outcome	References
MIGRAINE PREVENTION			
Open-pilot 3 months	10 episodic MO patients	−1.3 reduction in monthly attack frequency 5/10 patients satisfied	Gérardy et al. *Cephalalgia* 2009 (abstract) [27]
Multicentre, double-blind, randomized, sham-controlled 3 months	67 episodic MO patients (34 verum, 33 sham)	≥50% responder rate Verum: 38.1% Sham: 12.1%	Schoenen et al. *Neurology* 2013 [28]
Open 2 months	20 drug-naïve episodic MO patients	≥50% responder rate: 81%	Russo et al. *J Head Pain* 2015 [82]
Survey of prospective company registry	2313 migraineurs testing the Cefaly®	54.4% satisfied & willing to buy after a 58-day test 4.4% report adverse events (2.03%: local intolerance)	Magis et al. *J Head Pain* 2013 [30]
Open 4 months	23 chronic migraine patients with or without medication overuse	50% reduction in monthly migraine days: 35%	Di Fiore et al. *Neurol Sci* 2017 [83]
Open, multicenter, 3 months	Migraine patients not responding/intolerant to topiramate 31 episodic 6 chronic	50% responder rate: 1/31 2.6 headache days 3.9 days with acute medication	Vikelis et al. *BMC Neurol* 2017 [84]
Open, 10 sessions 1 month follow-up	60 migraine patients 31 other headaches 57 treated	50% reduction in attack frequency Decrease in intensity & duration	Przeklasa-Muszynska et al. *Neurol Neurochir Pol* 2017 [85]
Open 3 months	58 chronic migraine patients	Headache days: −24% (nonpermanent headache, n = 34); −5% (permanent headache, n = 24)	EHF 2017 ClinicalTrials.gov Identifier: NCT02342743
ATTACK TREATMENT			
Open-pilot Non-treated attacks	10 episodic MO patients 3 attacks	Attack outcome at 30 min: 12% – total relief 45% – partial relief 43% – no effect	Gérardy et al. *Cephalalgia* 2009 (abstract) [27]
Open Rescue for attacks of ≥72 h	16 episodic MO patients	46% reduction of headache 56% patients like to use it again	Kozminski. *Headache* 2014 (abstract) [86]
Open In-hospital 1 h treatment Attack duration ≥3 h	30 episodic MO patients	At 1 h: 57% reduction in head pain 77% of patients with 50% pain relief	Chou et al. *Neuromodulation* 2017 [32]
Internet survey by questionnaire	413 physician-diagnosed migraineurs Regular Cefaly® users	88.6% use the device in 71.8% of attacks 42.6% device-treated attacks with reduction of acute migraine drugs	Penning & Schoenen *Acta Neurol Belg* 2017 [31]
Multicentre, double blind, randomized, sham-controlled, In-hospital 1 h Attack duration ≥3 h	106 migraine patients (23% with aura) 52 verum 54 sham	At 1 h: VAS: −59% (sham −30%) 29% pain-free (sham: 6%) 63% of patients with 50% pain relief (sham: 31%)	Chou et al. 2017 [33]
Open label, at home, 2h Moderate to severe attacks of ≤ 4h duration	59 episodic migraine patients 48 eligible for mITT analysis	At 2 h: 35.4% pain-free 70.8% pain relief 23% 2–24 h sustained pain-freedom	Mann & Schoenen 2018 *AHS* (abstract) [34]

MO: migraine without aura; VAS; visual analogue scale; mITT: modified intention-to-treat.

high frequency TENS, resembling the Cefaly® stimulation protocols, more likely engage extrasegmental mechanisms such as activation of subcortical pain control centers [43].

We will review the evidence for peripheral, segmental and suprasegmental mechanisms possibly involved in the antimigraine eTNS effects.

3.1. Peripheral nervous system mechanisms

As opposed to the visceral afferents of the trigeminovascular system, somatic nociceptive afferents of the first division of the trigeminal nerve are not supposed to play a major role in migraine headache pathophysiology. Nonetheless, branches of meningeal nociceptive fibers were recently found to emerge at the level of cranial emissary canals and fissures and to innervate the cranial periosteum and muscles mainly in the temporal, parietal, and occipital areas [44]. Because of its anatomical position and its reduced surface, it seems thus unlikely that the device activates such extracranial meningeal afferents.

High intensity–low frequency TENS causes intense, but not uncomfortable, muscle contraction able to activate muscle afferents and to produce analgesia [40]. Given the small size of forehead muscles under the stimulator, this probably is not relevant for the device's antimigraine effects. Interestingly, in chronic migraine patients eTNS caused an increase of median frequency and amplitude of the electromyographic signal in anterior temporalis, auricularis posterior and middle trapezius muscles [45]. It

is doubtful that this is relevant for the mode of action of the device, the more so that there was no increase in frontalis muscle activity and that pericranial muscles have no role in the pathophysiology of chronic migraine [46].

3.2. Central effects

The changes induced by single or multiple sessions of eTNS on central nervous system activities are summarized in Table 2.

Several experimental studies have not confirmed the hypothesis that pericranial nerve stimulation might decrease trigeminal nociception by a segmental gate control. Stimulation of the greater occipital nerve increased, rather than decreased, activation by dural afferents of trigeminocervical nociceptive neurons in rats [47] and suboccipital 3 Hz nociceptive stimulation had no effect in humans on the nociceptive blink reflex (nBR), a surrogate marker of spinal trigeminal nucleus excitability [48].

By contrast, nBR amplitude and homotopic pain ratings were found lastingly diminished by supraorbital 1 Hz noxious stimulation in normal subjects and this was attributed to long-term depression of second order nociceptors in the spinal trigeminal nucleus [49]. An accompanying editorial [50] suggested that low frequency–high intensity acupuncture-like electrical stimulation might be able to attenuate the long-term potentiation of dorsal horn nociceptive synapses that contribute to hyperalgesia and allodynia and thus very promising for pain therapy.

Contrary to the previous study [49], eTNS uses high frequency stimuli. Nonetheless, when the effect of one 20-min session of stimulation (60 Hz, 16 mA) was tested on the nBR in 10 migraine patients recruited for the abovementioned pilot study [27], there was a mild, but significant decrease of nBR amplitude and a more pronounced decrease of habituation. One session of eTNS in migraine patients between attacks also significantly decreased amplitude of contact heat-evoked potentials (CHEPs) when they were obtained by thermonociceptive stimuli to the frontal skin, but not after stimulating the wrist [51]. The fact that eTNS reduces CHEPs homotopically suggests that it acts via trigemino-specific segmental or suprasegmental pathways. Since the eTNS effect is greater on CHEPs than on nBR, a suprasegmental mechanism could be more likely.

Along the same line, amplitude of laser heat evoked cortical responses was also significantly reduced after a 20min-session of real eTNS (250 µsec, 60 Hz, 16 mA) but not after sham stimulation (2 mA) both in migraineurs interictally and in healthy controls [52]. In this study, eTNS was associated with reduced evoked EEG activity in anterior cingulate cortex (ACC).

The confirmation that eTNS with this device might have central effects came from a double-blinded, cross-over, sham-controlled trial in 30 healthy volunteers measuring vigilance and attention with psychomotor tests at the end of a 20-min eTNS session at 2.5 or 120 Hz and of a session with sham stimulation (1 mA) [53] (see Table 2). In this study, there was a significant decrease in vigilance and attention during high frequency eTNS. Whether such an effect contributes to the therapeutic benefit of the eTNS device is uncertain, as for migraine therapy the stimulation frequencies used for acute and preventive treatment are lower, respectively 100 and 60 Hz. The commercialized device contains, however, a high frequency stimulation program (120 Hz) that certain patients use for relaxation.

Using fluoro-deoxyglucose (FDG)-PET we have analyzed changes in brain metabolism in 14 migraine without aura patients before, after one 20-min session and after 3 months of daily 20-min sessions of eTNS with the device (60 Hz, 16 mA) [54]. In patients compared to healthy controls, baseline glucose uptake was significantly decreased bilaterally in orbitofrontal (OFC), rostral anterior cingulate cortex (rACC), and temporal lobe. This hypometabolism was not modified after one eTNS session. However, in 10 patients who treated themselves for 3 months and were compliant to eTNS as revealed by the inbuilt software, monthly migraine days and attack frequency significantly decreased, and metabolism normalized in pretreatment hypometabolic areas

Table 2. Studies on central effect of eTNS with the Cefaly®.

CENTRAL EFFECTS OF eTNS WITH CEFALY®			
Study protocol	Method	Result	Authors
3-month treatment 60 Hz, 250 µs, 16 mA 10 episodic MO (compliant) 20 HC	FDG-PET baseline, after one 20-min session, & after 3 months of daily sessions	*After 1 session*: no significant change *After 3 months*: ↙ of baseline hypometabolism in OFC & rostral ACC	Magis et al. *Cephalalgia* 2017 [54]
2-month treatment 60 Hz, 250 µs, 16 mA 15 episodic MO 15 HC	fMRI BOLD non-noxious (41°C) or noxious (51°C) (THS)	*Before eTNS*: greater noxious THS-induced ACC activation in MO *After eTNS*: significant ↙ of ACC activation THS-induced ACC activation negatively correlated with attack frequency	Russo et al. *Front Neurol* 2017 [56]
Real: 20 min session 60 Hz, 250 µs, 16 mA Sham: 10 sec, 2 mA 17 episodic MO 21 HC	LEPs Frontal/hand stimulation LORETA analysis	↙N2P2 amplitude, ↙activity in ACC in MO & HC Reduced habituation in MO reversed by real& sham	Vecchio et al. *Cephalalgia* 2017 [52]
one 20-min session 60 Hz, 250 µs, 16 mA 15 episodic MO	CHEPs Frontal/hand	↙N2P2 amplitude of frontal CHEPs no change of hand CHEPs	Sasso D'Elia et al. *Cephalalgia* 2013 (abstract) [87]

FDG-PET: fluorodeoxyglucose positron emission tomography; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; fMRI BOLD: functional magnetic resonance imaging blood oxygen-level dependent; HC: healthy controls; THS: trigeminal heat stimulus; LEPs: laser evoked potentials; CHEPs: contact heat evoked potentials.

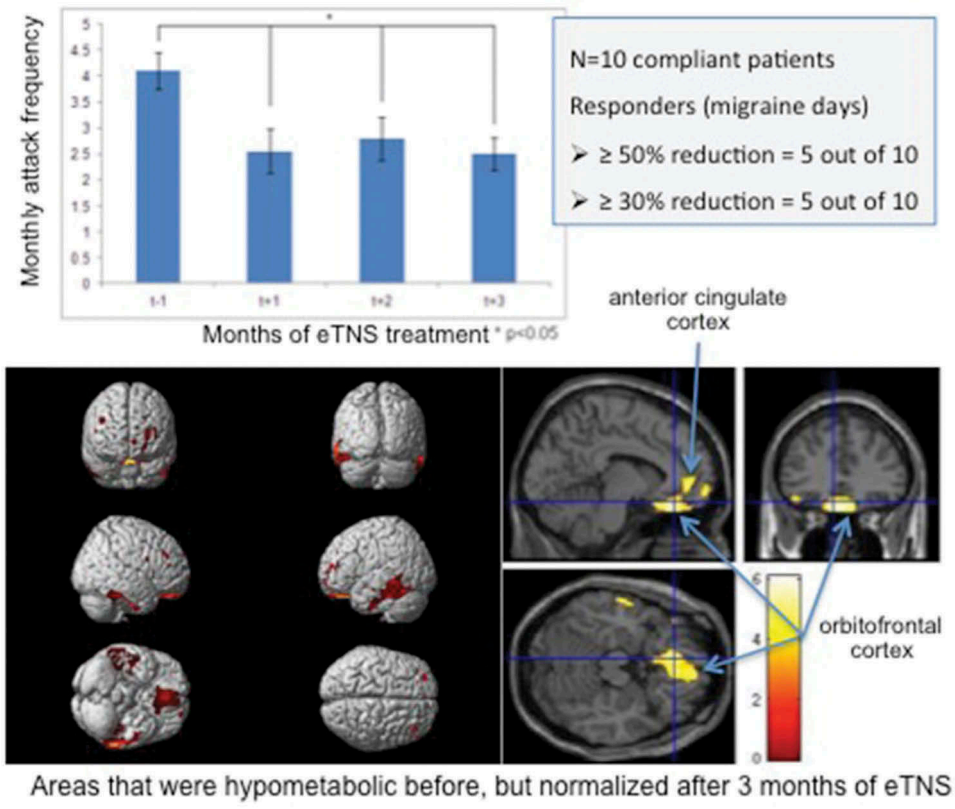

Figure 1. Histogram of changes in monthly migraine attack frequency before and after 1, 2, and 3 months of Cefaly® eTNS treatment in 10 compliant migraine without aura (MO) patients. Brain areas with significantly different glucose uptake on FDG-PET overlaid over an MRI anatomical map. Anterior cingulate cortex, orbitofrontal cortex and temporal lobe were hypometabolic in patients before treatment compared to healthy controls; all these areas normalized after 3 months eTNS.

(Figure 1). The change in rACC metabolism combined to the reduction of migraine attack frequency overtime during eTNS may be the consequence of a slow central neuromodulatory action, similar to that of other peripheral nerve stimulations (see [50] for a review). Interestingly, Russo et al. [55] found that blood oxygen-level dependent (BOLD) activation in perigenual ACC (pgACC) by a noxious heat stimulus on the cheek was significantly greater in migraine without aura patients than in healthy volunteers. In a therapeutic study of the eTNS device, the same authors [56] found that 2 months of eTNS in 20 migraineurs significantly reduced the noxious heat-induced BOLD activation in pgACC as well as migraine attack frequency proportionally to the functional magnetic resonance imaging (fMRI) changes (Figure 2).

Between attacks migraine patients have smaller early bursts of high-frequency oscillations (HFO1) embedded in somato-sensory evoked potentials than healthy controls [57]. HFO1 are thought to be generated by action potentials in thalamocortical afferents and hence to reflect interictal thalamocortical dysrhythmia in migraine. Late HFO (HFO2) are due to cortical (inhibitory) interneuron discharges and of normal amplitude in migraine. Immediately after one 20-min session of eTNS, SSEP HFO1 are significantly increased for less than 5 min, while there is no effect on HFO2 (Figure 3) [58]. Whether the interictal low thalamocortical activity may be related to the low metabolism in medial frontal cortices, and its normalization by eTNS to the metabolic enhancement found after eTNS, remains to be determined. It is worth mentioning, however, that the electrophysiological changes were recorded after a single eTNS session, whereas the metabolic changes were found after chronic treatment, i.e. 3 months of daily eTNS.

4. ACC: the common denominator?

Taken together, the studies described above and summarized in Table 2 suggest that eTNS with the device acts predominantly at suprasegmental levels by modulating activity in medial frontal cortical areas comprising the anterior cingulate and OFC cortices. These areas exert multiple functions related to decision-making, mood and the affective dimensions of pain controlling in particular individual levels of central pain modulation in healthy subjects [59]. They were found to dysfunction in chronic migraine [60], medication overuse headache [61], and chronic cluster headache [62].

Schwedt et al. [63] have reviewed the data obtained with functional MRI in migraine. An update of the literature review on the topic depicted in Table 3 shows that the ACC, a major target of eTNS as described above, was found abnormal in a number of studies assessing brain morphology, connectivity, or function. The pgACC is of particular interest, as its activity was found modified by eTNS in three studies with convergent results but with different methods, FDG-PET [54], fMRI [56], and pain-related evoked potentials [52]. The pgACC has been implicated in various functions and diseases. For instance, it plays a role in

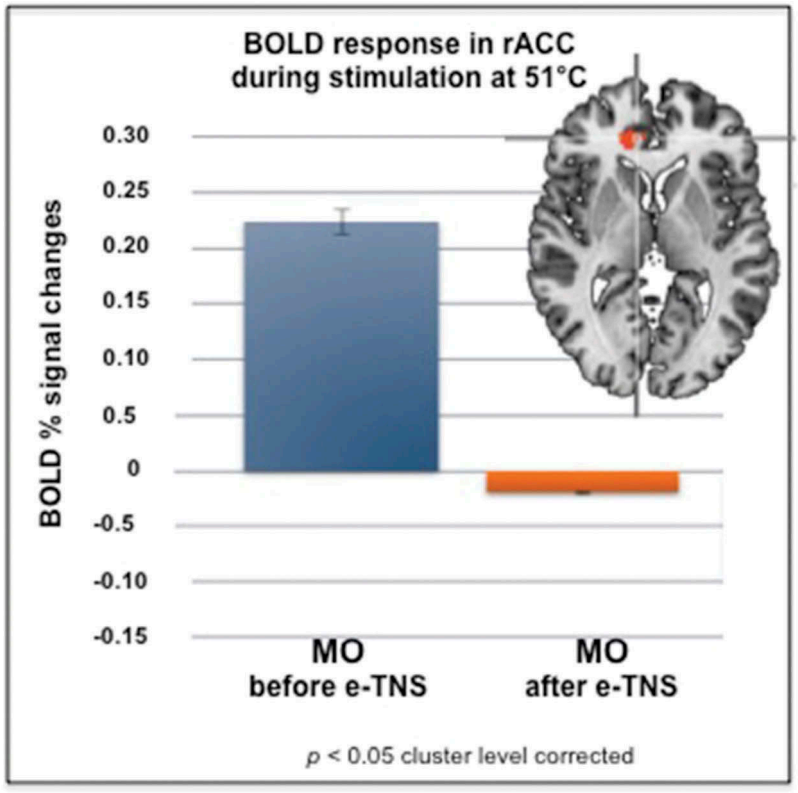

Figure 2. BOLD responses induced in right ACC (Talairach coordinates (*x, y, z*: 12, 35, 7) by a thermo-nociceptive stimulus are increased in migraine without aura (MO) patients ($n = 20$) before eTNS. They are significantly reduced after 2 months of daily eTNS. Insert: T-map of statistically significant differences between MO and healthy controls overlaid onto a Talairach transformed Colin-27 T1 high-resolution anatomical template. Bar graphs of percent BOLD signal changes during noxious trigeminal heat stimulation at 51°C in MO patients before and after eTNS (modified after Russo et al. 2017 [56]).

several psychiatric disorders in which its dysfunction is associated with a variant in the CACNA1C gene [64], but also in the self and resting state activity in the default mode network where it is modulated by glutamate [65,66]. With regard to migraine, however, the most relevant pgACC function is the one related to pain control where it mainly seems to be involved in the affective and emotional dimension. The pgACC was overall less activated on fMRI in chronic pain patients than in healthy controls in a paradigm where subjects had to estimate perceived pain intensity on pictures depicting human limbs in painful and non-painful situations [67]. It is thought to mediate in part the analgesic effects of motor cortex stimulation [68] and to play a pivotal role in the central opioïdergic pain control system. The pgACC is rich in opioid receptors and selectively activated during opioid [69,70], but also placebo analgesia [71], providing evidence that both analgesic modalities are mediated by activation of descending antinociceptive pathways.

Admittedly, abnormalities of the pgACC are not specific to migraine. In cluster headache, in particular, the pgACC was found hypometabolic outside of a bout but its metabolism increased during a bout [72]. The same authors using PET with the opioid receptor ligand [11C]diprenorphine found an inverse relationship between duration of the cluster headache disorder and opioid receptor availability in pgACC and ipsilateral hypothalamus [73]. In drug-resistant chronic cluster headache patients, we have shown in a FDG-PET study that metabolism in the pgACC is increased in responders to chronic ONS compared to nonresponders [61]. In migraine and cluster headache, both neurovascular disorders, it remains controversial whether the dysfunction of descending pain control systems is a primary causative phenomenon or secondary to repeated painful attacks. Interestingly, both cluster headache [74] and migraine [75] are accompanied by hypothalamic activation as a possible generator of an attack. The pgACC has strong connectivity with the hypothalamus [76], which might thus explain why it is involved in both disorders.

Finally, the facts that involvement of the pgACC seems not specific for migraine, nor limited to pain control, and that eTNS can change its activity and thalamocortical circuits, may explain why pericranial neurostimulation, including eTNS, was reported to have also therapeutic effects in tension-type headache [77], fibromyalgia [78], depression [79], and epilepsy [80]. Given that transcranial stimulation methods are able to change activity in underlying cortical and subcortical structures including the pgACC, it remains to be determined if they have therapeutic potentials in migraine. Based on this rationale and the above-mentioned study showing pgACC activation in refractory chronic cluster headache patients ameliorated by ONS [62], we have recently found in a proof-of-concept trial that transcranial direct current stimulation (tDCS) with a montage targeting the pgACC also has beneficial therapeutic effects in those patients [81].

5. Expert commentary

We have reviewed published evidence showing that eTNS with this device is effective for the preventive and the acute treatment of migraine. Effect size for prevention is

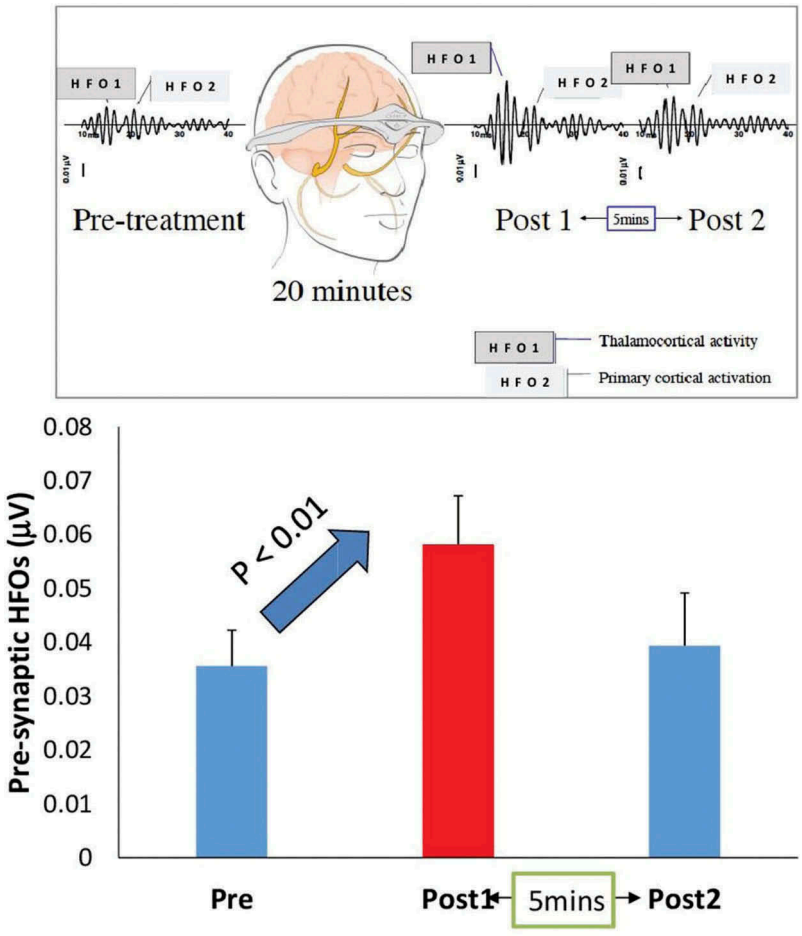

Figure 3. Upper: illustrative recording in a migraine patient of high frequency oscillations (HFO, 450–750Hz) in somato-sensory evoked potentials before (pretreatment) and immediately (Post 1) and 5 min after (Post 2) one 20-min session of eTNS with the Cefaly®. HFO1: early burst reflecting thalamocortical activity; HFO2: late burst reflecting discharges of inhibitory cortical neurons.

Lower: bar graph showing pre- and post-eTNS changes in HFO1 in a group of 10 migraine patients between attacks (mean ± SEM).

somewhat lower compared to the available most effective preventive drugs, but tolerability is far better. Published studies on the mechanisms of action of eTNS suggest that modulation of central brain areas involved in pain control, in particular of the ACC, either directly or via changes in thalamocortical activity, could be pivotal for the beneficial clinical effects. A segmental action on the trigeminal system in the brain stem may contribute to the beneficial acute eTNS effect. We have analyzed the imaging literature in migraine and were struck by the fact that the ACC was found abnormal in most studies, be they focused on its morphological, connectivity or functional properties. The pgACC may thus be the crucial mediator of the device's therapeutic effects, which may explain why eTNS can mitigate other painful and non-painful conditions in which this brain area has a pathophysiological role. Given that non-invasive neurostimulation at very different sites such as mastoids [20], upper limb [22] or vagus nerve in the neck [21], appears to have comparable beneficial effects in migraine, it seems worthwhile to explore modulation of ACC as a common mechanism of action for noninvasive peripheral neurostimulation.

6. Five-year view

Several clinical trials with this eTNS device are ongoing or planned, exploring, for example, its utility in treating headache in the emergency ward, in preventing the full development of a migraine attack when applied at the very beginning of an attack, or in mitigating withdrawal headache during the weaning period in medication overuse headache. There are also plans to conduct a randomized controlled trial in tension-type headache, but also in other chronic pain syndromes like fibromyalgia and in epilepsy. Evidence of efficacy should be sought for the suboccipital eTNS that has shown promising results in open trials of chronic migraine. The possible advantage of stimulating simultaneously or alternatively the frontal and suboccipital regions has to be investigated. It is also of great interest to develop a device combining eTNS with transcranial direct current stimulation, since the latter allows direct modulation of the cortical responsivity known to be abnormal in migraine while the former seems to act more generally on areas of the limbic and pain systems.

Despite the recent avenue of novel pharmacotherapies for migraine with an excellent efficacy/tolerability profile like the monoclonal antibodies against CGRP or its receptor, it is likely that a niche for noninvasive

Table 3. Functional imaging studies showing anterior cingulate cortex alterations in migraine.

ANTERIOR CINGULATE CORTEX ALTERATIONS IN MIGRAINE			
Study protocol	Method	Result	Authors
20 patients with trigeminopathic pain before & after 30min electrostimulation of the trigeminal ganglion	H_2O^{15}-PET	↗ regional cerebral blood flow (rCBF) in rostral ACC Contralateral caudal ACC rCBF encodes pain	Willoch et al. *Pain* 2003 [88]
Meta-analysis 222 migraineurs 230 HC	Voxel-based morphometry MRI	↙ gray matter in ACC (& posterior insular-opercular regions, prefrontal cortex	Dai et al. *Neuroscience* 2015 [89]
16 interictal EM 16 HC	fMRI BOLD non-noxious (41°C) or noxious (51/53°C) (THS)	↗ ACC activation by 51°C THS in MO	Russo et al. *J Neurol* 2012 [55]
15 interictal EM 15 HC	fMRI BOLD after nasal ammonia	↙ACC activation	Aderjan et al. *Pain* 2010 [90]
21 interictal EM 21 HC	fMRI connectivity (ROI: ACC)	↗ ACC connectivity with middle temporal, orbitofrontal & DLPF cortices	Jin et al. *NMR Biomed* 2013 [91]
20 chronic migraine 20 HC	fMRI connectivity (ROI: ACC)	ACC connectivity with pain matrix areas in sensory discriminative, cognitive & integrative domains	Schwedt et al. *Headache* 2013 [92]
18 interictal EM	fMRI low frequency fluctuations & connectivity	↙ low frequency fluctuations in rostral ACC ↗ rostral ACC connectivity with frontal & parietal lobes	Xue et al. *NMR Biomed* 2013 [93]
40 interictal EM 40 HC	fMRI connectivity ROI: basal ganglia	↗ ACC connectivity with nucleus accumbens	Yuan et al. 2013 [94]
26 interictal EM 26 HC	fMRI regional homogeneity (whole brain)	↙ reg homog in ACC negatively correlated with disease duration	Yu et al. 2012
40 interictal EM 20 HC			Zhao et al. 2013 [95,96]
43 interictal EM 43 HC	fMRI (90 ROI)	in ACC & negative correlation with disease duration	Liu et al. 2012 [97]
10 high frequency (HF) interictal EM 10 low frequency (LF) interictal EM	fMRI connectivity ROI: postcentral gyrus, anterior insula, temporal pole, ACC	↗ ACC connectivity with frontal pole, temporal pole, inferior temporal gyrus, pulvinar, parahippocampal gyrus in HF compared to LF	Maleki et al. 2012 [98]
14 interictal EM 14 HC	fMRI frontoparietal network	↙ ACC connectivity	Russo et al. 2012 [99]
26 intrictal EM 26 HC	fMRI regional homogeneity	↙ ACC homogeneity	Yu et al. 2012 [100]
21 interictal EM 21 HC	fMRI voxel-mirrored homotopic connectivity ROI: ACC	↙ ACC interhemispheric connectivity ↗ ACC connectivity with OFC	Yuan et al. 2012 [101]
17 interictal EM 17 HC 5 EM with allodynia 5 EM without allodynia	fMRI ROI: periaqueductal gray	↙ connectivity with ACC	Mainero et al. 2011 [102]
25 CM (18 ictal) 24 EM (3 ictal) 25 HC	MRSI ROI: medial brain walls	CM: ↙ NAA in rACC Altered NAA correlation thalamus – ACC, lACC-rACC NAA: CM< EM< HC EM interictal: ↙ myo-inositol in lACC negatively correlated with depression scores Ictal: ↙ NAA & creatine lACC	Niddam et al. *Brain* 2017 [103]
13 CM (interictal) 16 MOH (interictal) 16 HC	fMRI salience network intranetwork functional connectivity	CM & MOH: Shared aberrant intranetwork connectivity within the salience network, including dACC	Androulakis et al. *Cephalalgia* 2017 [104]
18 MA 33 MO 32 HC	fMRI resting state: five frequency bands by discrete wavelet decomposition	MA vs. MO: ↗ amplitude of resting-state activity in ACC	Faragò et al., *JHP* 2017 [105]

rCBF: regional cerebral blood flow; EM: episodic migraine; ROI: region of interest; DLPFC: dorsolateral prefrontal cortex; CM: chronic migraine; MRSI: magnetic resonance spectroscopy imaging; NAA: N-acetylaspartate; MOH: medication overuse headache; MA: migraine with aura.

neurostimulation methods as alternative or add-on therapies in primary headaches will persist. The future will determine which of the various methods is most valuable and for each headache type.

Key issues

- External trigeminal neurostimulation (eTNS) with the Cefaly® device has evidence for a preventive therapeutic effect in episodic migraine as well as for an abortive effect during migraine attacks. There is circumstantial evidence for its beneficial effect in chronic migraine and tension-type headache.
- Its efficacy/tolerability profile is excellent, exceeding that of most drug treatments for headaches.
- Available data cannot exclude that eTNS device may have an analgesic effect via a gating effect in the trigeminal pain pathway.
- Recent imaging studies, however, suggest that its predominant acute and chronic effect is modulation of activity

in the anterior cingulate cortex (ACC), a crucial limbic area belonging to the salience/pain network.
- A comprehensive literature review indicates that the ACC is precisely an area found abnormal in most morphological or functional imaging studies of migraine.

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Declaration of interest

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