Migraine treatment with external trigeminal nerve stimulation: current knowledge on mechanisms

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Abstract

Available pharmacological migraine treatments have incomplete efficacy and many of them may have intolerable adverse effects. There is thus a need for alternative, more efficient and better tolerable therapies. Pericranial nerve stimulation methods represent such an alternative. Thanks to technological advances, non-invasive, user-friendly, transcutaneous stimulators have been developed recently and are applicable in patients with any level of disability. In particular, supraorbital external trigeminal nerve stimulation (eTNS) with the Cefaly® device was found effective for migraine prevention in several studies. There is circumstantial evidence that the device is also useful for migraine attack treatment.

The mode of action of eTNS in migraine is not fully understood. Like extra-cephalic transcutaneous electrical nerve stimulation (TENS), eTNS may have segmental "gate control" mechanisms as well as supra-segmental actions. Scarce evidence for a segmental mechanism comes from studies of the nociceptive blink reflex (nBR). A single session of eTNS in migraine patients during an attack relieves pain transiently, but has no effect on cerebral metabolism. Conversely, after several months of eTNS with the Cefaly®, metabolism, assessed with FDP-PET, increases in pre-treatment hypometabolic medial prefrontal cortical areas, including anterior cingulate cortex, while trigeminal noxious heat-induced fMRI BOLD hyperactivation of the latter normalises. These metabolic changes are accompanied by a significant decrease in monthly attack frequency in compliant patients.

Taken together, available data suggest that mode and site of Cefaly®'s action may differ between its acute and preventive anti-migraine effects. While it may relieve headache during an attack by a segmental, somatic afferent-induced blockade of nociceptive trigeminovascular afferents in trigeminal nucleus caudalis, its preventive effect more likely depends on a slow modulatory supra-segmental mechanism that normalises activity in cortical areas controlling pain and its behavioural aspects.

Key words: Migraine, acute treatment, preventive treatment, external trigeminal nerve stimulation, mode of action

Introduction

Migraine management includes acute and preventive treatments. While acute treatments aim at interrupting an attack and restore normal function (1), preventive treatments have the disease-modifying objective of reducing attack frequency and severity (2). Currently, migraine is mostly managed with pharmacologic treatments. The most commonly used drugs to interrupt migraine attacks are analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and triptans (3). Effective preventive drugs include beta-blockers without intrinsic sympathicomimetic activity, calcium channel blockers, sartans and the anti-convulsants topiramate and valproate (4), as well as nutraceuticals like riboflavin and co-enzyme Q10 (5).

Besides the latter, most preventive anti-migraine drugs are associated with moderate to severe side effects, have contraindications and only partial efficacy leading frequently to dissatisfaction and discontinuation by the patients (6, 7, 8). Consequently, 80% of patients are willing to change their current medication for a treatment with similar efficacy but fewer side effects (9). Last but not least, in patients with frequent and/or prolonged migraine attacks, excessive consumption of acute anti-migraine drugs may lead to headache chronification, i.e., medication overuse headache, which worsens the patients' condition (10)

1. The Clinical Evidence

The shortcomings of pharmacological migraine management underscore the need for better treatments and have created a niche for non-pharmacologic therapies such as neurostimulation. Peripheral nerve stimulation (PNS) is not a novel approach to treat headaches (see 11 for review). Percutaneous nerve stimulation was reported effective for the treatment of various headaches since the 90s (12, 13). Occipital nerve stimulation (ONS) was beneficial for chronic migraine in sham-controlled trials, although the global effect size was modest (14, 15, 16). The combination of percutaneous ONS and supraorbital nerve stimulation (SNS) was claimed to have a better effect, but randomized controlled trials are lacking (17). The common drawback of these neurostimulation methods is that they are invasive and applicable only to the most disabled patients with frequent, severe and drug-refractory migraine (18).

The development of non-invasive transcutaneous stimulators opened the neurostimulation field to all migraine patients without consideration of disability or drug-refractoriness (see 19 for a review). The first studies showing beneficial effects in various headache types were published as early as 1985 (20, 21, 22, 23), the single-blinded placebo-controlled trial by Solomon and Guglielmo (20) being the most convincing.

It took 2 decades before technological advances allowed developing a portable, user-friendly and more effective external trigeminal stimulator (eTNS), the Cefaly® (Cefaly Technology sprl, Grâce-Hollogne, Belgium). The Cefaly® device stimulates transcutaneously supraorbital branches of the ophthalmic nerve and in the randomised, sham-controlled, blinded PREMICE trial (24), effective stimulation (pulse width 250µs, 60Hz stimulation frequency, 16mA intensity, 20-min daily application) was found clearly superior to sham stimulation (pulse width 30µs, 1Hz frequency, 1mA intensity) for the prevention of episodic migraine. After 3 months of treatment, mean number of monthly migraine days was significantly decreased and 38.1% of the 34 effectively treated patients had a $\geq$ 50% reduction in migraine days compared to 12.1% in the 33 sham-treated patients. There were no adverse events. For comparison, in the pooled

analysis of topiramate RCTs, the 50% responder rate was 45.3%, but 50% of patients had drug-related side effects and 1 out of 4 patients abandoned treatment because of intolerable adverse effects (25). As a consequence of the PREMICE trial, in March 2014 Cefaly® was the first medical device approved by the FDA for the prevention of migraine. Its beneficial preventive effect in low-frequency migraine was also suggested by a small open study in 24 drug-naive migraineurs (26) and a prospective registry involving 2,313 patients showed that eTNS is a well tolerated and safe therapy with mild adverse events reported by only 4.3% of patients (27).

Although in clinical practice many patients report using Cefaly® during migraine attacks with a beneficial effect on headache and disability, only limited evidence is available for its efficiency in acute migraine treatment published in abstracts. In a pilot trial of 10 episodic migraine patients who treated 3 successive attacks with the device, total relief without rescue medication was obtained in 12% of attacks at 30 minutes, incomplete relief with rescue medication in 42.5% and no effect in 45.5% (28). In an open study of 16 patients, the Cefaly® device was effective and well-tolerated as rescue therapy for migraine attack symptoms present since at least 72 hours; it reduced the migraine headache on average by 46%, and 56% of patients declared they would like to use the device again (29). In another open study, Chou et al. (30) treated 30 patients during an attack in the hospital for 1 hour, which resulted on average in a 57% decrease of headache intensity. The sham-controlled trial with a similar protocol is about to be completed (see table 1). We recently published the results of an Internet survey on migraine attack treatment with the Cefaly® in 463 regular users using a structured questionnaire: 88.6% of them reported using the device in 71.8% of their attacks; the use of the device allowed a reduction of acute medication intake in 42.6% of attacks (31).
The precise mode of action of pericranial neurostimulation methods in migraine remains to be determined. Recent neuroimaging studies, however, may shed light on possible relevant mechanisms.

MIGRAINE PREVENTION

Study protocol	Number of patients	Outcome	References
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) (28)
Multicenter, 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 (24)
Open 2 months	20 drug-naïve episodic MO patients	≥ 50% responder rate: 81%	Russo et al. J Head Pain 2015 (26)

Survey of prospective company registry	2,313 migraineurs testing the Cefaly®	54.4% satisfied & willing to buy after a 58-day test 4.4% report adverse events (2%:local intolerance)	Magis et al. J Head Pain 2013 (27)
Open *3 months*	*Prevention in 50 chronic migraine patients*	*On-going*	*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) (28)
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) (29)
Open In-hospital 1h treatment Attack duration ≥ 3h	30 episodic MO patients	At 1 hour: 57% reduction in head pain 77% of patients with 50% pain relief	Chou et al. Headache 2016 (abstract) (30)
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)
Multicenter, double blind, randomized, sham-controlled, in-hospital 1hour	*90 episodic MO patients*	*On-going*	*ClinicalTrials.gov Identifier: NCT02590939*

Table 1: Synopsis of published and on-going clinical studies of external trigeminal nerve stimulation with the Cefaly® device in migraine. MO: migraine without aura. Italics: on-going trials.

2. Possible Mechanisms of Action

The initial rationale for the use of pericranial nerve stimulation in migraine postulated that convergence of somatic afferents from the trigeminal or the C2 territories with visceral trigeminovascular afferents on spinal trigeminal nucleus 2nd order nociceptors might block ascending impulses in the pain pathway. Like transcutaneous electrical nerve stimulation (TENS) known to relieve neuropathic pain since many years (32), it was thought that peripheral nerve stimulation could block nociceptive activity at the segmental level via activation of large Aβ afferents according to Melzack & Wall's gate control theory (33, 34). While this might be true for conventional low intensity-high frequency TENS, acupuncture-like high intensity-low frequency TENS and high intensity-high frequency TENS, resembling the Cefaly® stimulation pattern, are more likely to engage extrasegmental mechanisms like activation of subcortical pain control centres (35). We will successively examine the evidence for a segmental and a supra-segmental mode of action of eTNS in migraine therapy.

2.1. Peripheral mechanisms

The stimuli generated by eTNS generate nerve impulses that can in theory collide with noxious orthodromic afferent signals and extinguish them. This is more likely when Aδ fibers are activated by high intensity stimulation. Such a mechanism cannot play a significant role in migraine where somatic nociceptive afferents of the ophthalmic nerve are not supposed to be involved in headache generation, contrary to the visceral afferents of the trigeminovascular system. It was found recently, however, that branches of meningeal nociceptive fibers emerge at the level of cranial emissary canals and fissures to innervate extracranial structures like periosteum and muscles (36). These fibers have been described in the temporal, parietal and occipital areas and originate from the mandibular and maxillary portions of the trigeminal ganglion, not from the ophthalmic division. Due to the anatomical position and the small surface of its supraorbital electrode, the Cefaly® device is unlikely to activate significant numbers of these extracranial meningeal afferents.

High intensity-low frequency TENS over muscles produces strong but comfortable muscle contraction that can activate muscle afferents to elicit analgesia (35). Interestingly, quantitative electro-myography (EMG) recordings in 23 chronic migraine patients during eTNS with the Cefaly® showed an increase of median frequency and amplitude of the myo-electrical signal in anterior temporalis, auricularis posterior, and middle trapezius muscles, but not in frontalis (37). The significance of this finding for the mode of action of the device is doubtful, the more so that it is unlikely that pericranial muscle activity plays a pathogenic role in migraine (38).

2.2. Segmental mechanisms

The hypothesis that pericranial nerve stimulation would be able to decrease trigeminal nociception by a segmental mechanism comparable to the gate control theory was not confirmed in several experimental studies. In rats, stimulation of the greater occipital nerve increased, rather than decreased, central excitability of 2nd order nociceptors activated by dural afferents in the trigemino-cervical complex (39). In humans, low frequency (3Hz) nociceptive stimulation of the greater occipital nerve had no effect on amplitude of the nociceptive blink reflex (nBR), a surrogate marker of spinal trigeminal nucleus excitability (40). By contrast, 1Hz noxious stimulation of the supra-orbital skin

induced a long-lasting depression of nBR amplitude and homotopic pain ratings in normal subjects, which was thought to be due to long term depression of 2nd order nociceptors in the spinal trigeminal nucleus (41). In an accompanying editorial, Cruccu and Truini (42) suggest that low frequency-high intensity acupuncture-like electrical stimulation could be a great opportunity in pain therapy, because it might attenuate the long-term potentiation of dorsal horn nociceptive synapses that contribute to hyperalgesia and allodynia.

Unlike Aymanns et al.'s study (41), eTNS with Cefaly® uses high frequency stimulation. Nonetheless, in the abovementioned pilot study (28), we tested the effect of one 20-min session of stimulation with the device (60Hz, 16mA) on amplitude and habituation of the nBR in 10 migraineurs. Immediately after the stimulation, there was a mild, but significant decrease of nBR amplitude and a more pronounced decrease of habituation (Fig. 1)

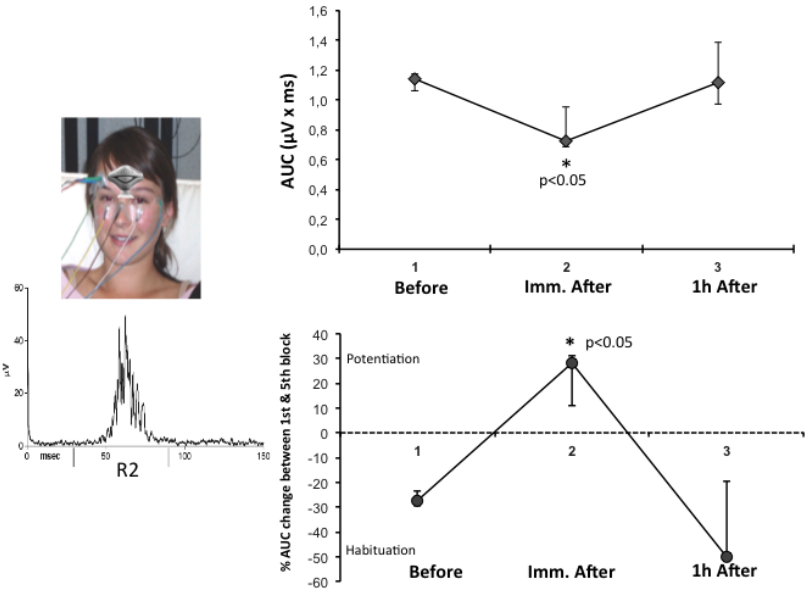

Figure 1: nBR changes after one 20-min session with the Cefaly® (60Hz, 16mA) (set-up and an illustrative recording on the left). Upper right: histogram of changes in area under the curve (AUC-average of 5 rectified responses) immediately after and 1h after the eTNS session. Lower right: histogram of change in AUC over 3 successive blocks of 5 averaged responses before and after eTNS.

In another group of 15 migraine without aura patients between attacks, we also recorded contact heat-evoked potentials (CHEPs), a thermonociceptive cortical evoked response, before and after a single session with the Cefaly®. As shown in Figure 2, eTNS significantly decreased the amplitude of the CHEP obtained by a heat stimulus to the frontal skin, but not that of the CHEP elicited by stimulation at the wrist. The eTNS-induced decrease of the thermonociceptive potential is thus homotopic, suggesting that eTNS modulates nociception via trigemino-specific segmental or supra-segmental pathways. In view of the greater effect on CHEP than on nBR, a supra-segmental mechanism seems more likely.

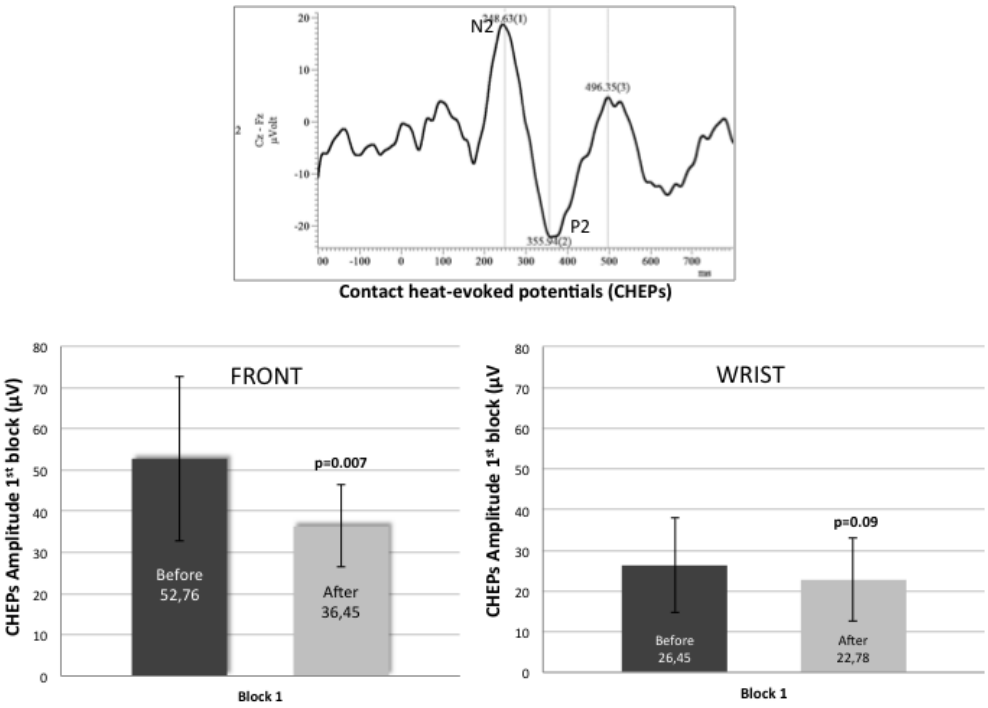

Figure 2: Contact heat-evoked potential (CHEP) recorded over the scalp after heat stimulation at the front or at the wrist in 15 migraine without aura patients. Upper panel: illustrative recording of 5 averaged responses in one patient. Lower panels: amplitude of the 1st block of 5 responses before and immediately after one 20-min session of eTNS (left: heat stimulation of the front; right: heat stimulation at the wrist.

2.3. Supra-segmental mechanisms

The 1st indication for a central effect of the Cefaly® came from a double-blinded, cross-over, sham-controlled trial in 30 healthy volunteers that assessed its effects on psychomotor tests (43). This study found that reaction time in a psychomotor vigilance task and score on the Fatigue Visual Numeric Scale were significantly increased after one 20-min session of eTNS at 120Hz, while critical flicker fusion frequency was decreased, which suggested that the device had produced a mild, transient sedative effect. Whether such an effect contributes to the therapeutic benefit of Cefaly® is uncertain, the more so that in clinical practice the highest stimulation frequency used is 100Hz, the protocol recommended for attack treatment.

We have recently published the results of a fluoro-deoxyglucose (FDG)-PET study that analysed brain metabolism in 14 patients suffering from episodic migraine without aura before, immediately after one 20-min session and after a 3-month treatment period of daily 20-min sessions of supraorbital eTNS with the Cefaly® (60Hz, 16mA) (44). Baseline FDG-PET revealed a significant hypometabolism of orbitofrontal (OFC), rostral anterior cingulate cortices (rACC) and middle temporal lobe, compared to a control group of healthy volunteers. There was no significant metabolic change after one session of eTNS. By contrast, after 3 months of daily stimulation, frequency of monthly migraine days significantly decreased in 10 compliant patients who performed at least 30% of the 90 recommended sessions. An in-built software that records number of sessions and time of use monitored compliance. In these patients the OFC and rACC hypometabolism was significantly reduced after 3 months (Fig. 3).

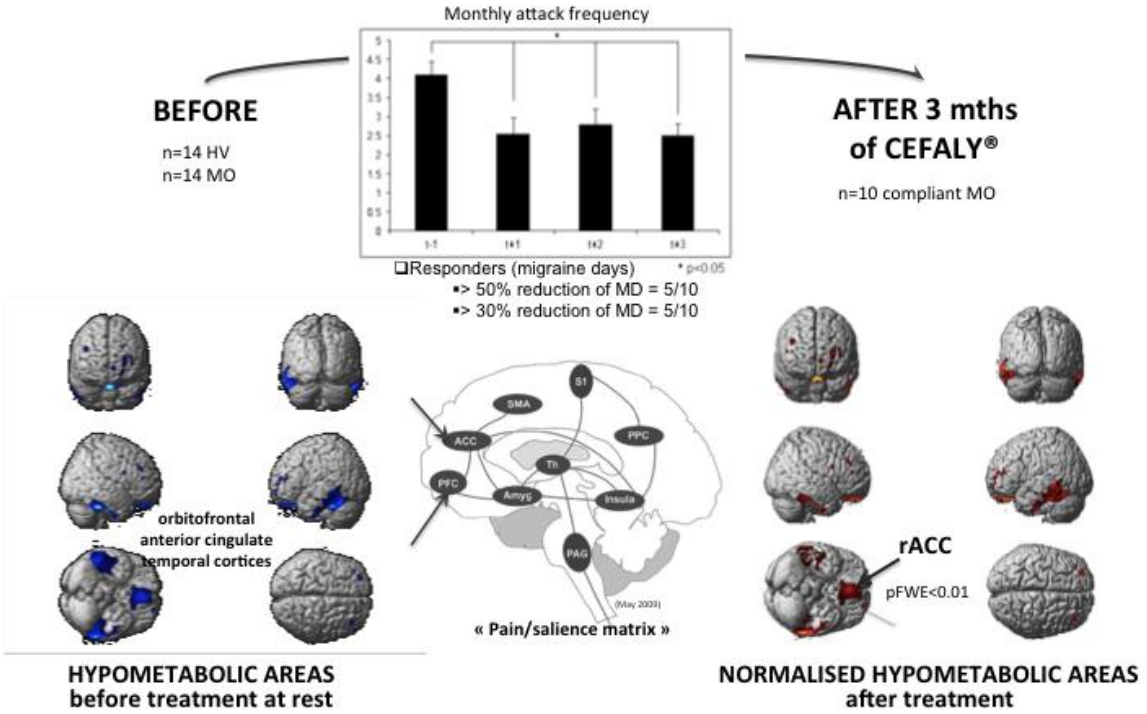

Figure 3: Histogram of changes in monthly migraine attack frequency before and after 1, 2 and 3 months of Cefaly® treatment in 10 out of 14 compliant migraine without aura (MO) patients. Brain areas with a significantly different glucose uptake overlaid over an MRI anatomical map: hypometabolic areas in MO before treatment compared to 14 healthy volunteers (HV) (left panel); areas with increased metabolism after treatment in 10 compliant MO patients (right panel). In the middle: schematic representation of brain areas belonging to the pain/salience matrix after May 2009. rACC: rostral anterior cingulate cortex; PFC: medial prefrontal cortex. pFWE: p corrected for multiple comparisons (family wise error corrected) (modified after 44).

The change in OFC/rACC metabolism and the progressive reduction of migraine attack frequency with eTNS might suggest that the treatment exerts a slow central neuromodulatory effect, akin to other peripheral nerve stimulations (see 45 for a review). Interestingly, Russo et al. (46) have reported in the perigenual part of the ACC greater fMRI BOLD activation after trigeminal noxious heat stimulation in migraine patients than in healthy volunteers. In a follow-up study, the same authors (47) found that this noxious heat-induced BOLD activation was significantly reduced after 2-month eTNS with the Cefaly® in 16 MO patients (Fig. 4).

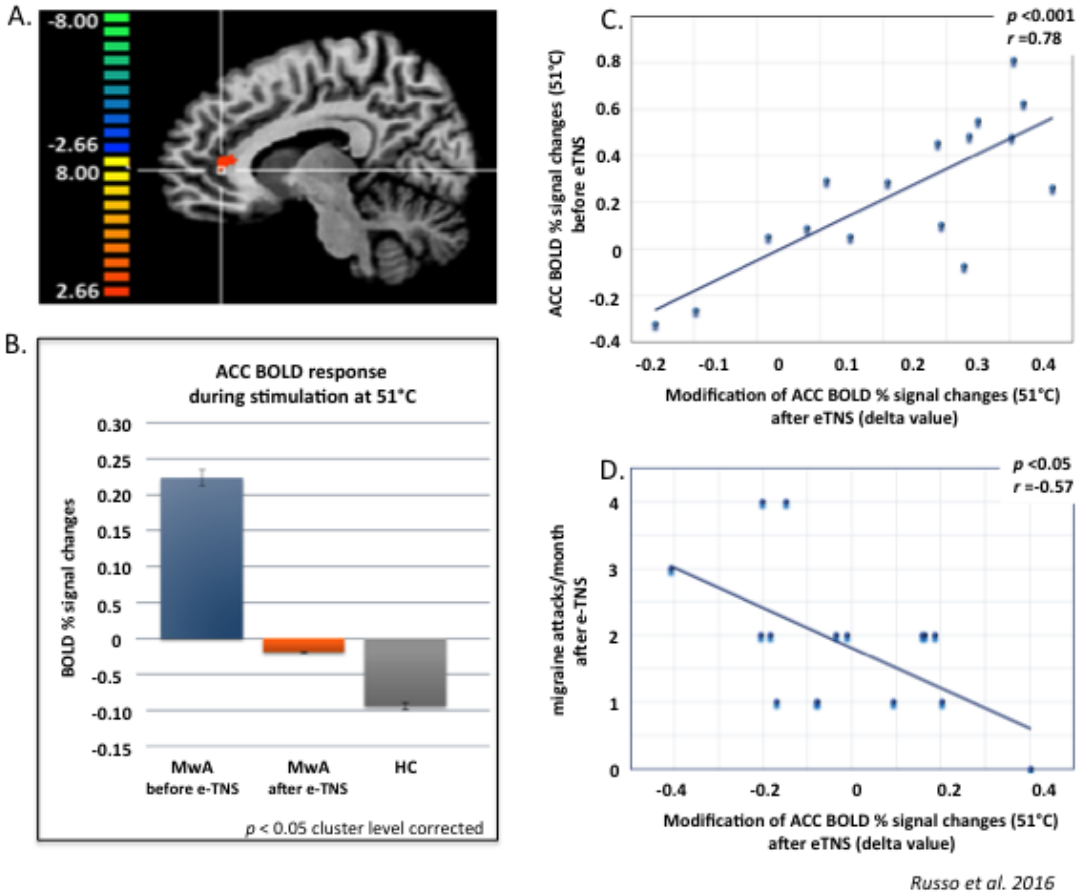

Figure 4: Significantly different BOLD-response between MwA patients before eTNS treatment and HC and between MwA patients before and after eTNS treatment. A) T-map of statistically significant differences between groups overlaid onto a Talairach transformed Colin-27 T1 high-resolution anatomical template; B) Bar graphs of percent BOLD signal changes at Talairach coordinates (x, y, z): right ACC= 12, 35, 7 during noxious trigeminal heat stimulation at 51° C in MwA patients before and after eTNS treatment and the HC group. C) Scatterplot showing significant correlations between ACC BOLD response to noxious heat before eTNS (y-axis) and the modification of the heat-induced ACC BOLD response after eTNS (i.e. the "delta value") (x-axis). D) Scatterplot showing significant correlations between modifications of the heat-induced ACC BOLD response changes after eTNS (x-axis) and post-treatment migraine attack frequency/month (y-axis) MwA: migraine without aura. HC: healthy controls (modified after 47).

Functional neuroimaging studies in chronic cluster headache (48) and chronic migraine patients (49) have shown that percutaneous occipital nerve stimulation is able to increase metabolism in central areas belonging to descending pain control centres, including the ACC, but leave unchanged disease-specific structures like the hypothalamus in cluster headache or the dorsal pons in migraine. By the same token, long electrical stimulations of the trigeminal ganglion in patients with trigeminal neuropathic pain increased regional blood flow in the ACC, OFC and medial frontal cortices, which was correlated with pain relief (50). Finally, opioid and placebo analgesia are also associated with increased

activity of OFC and rACC, suggesting a common underlying mechanism (51).

A last piece of experimental evidence arguing in favour of a supra-segmental action of eTNS comes from a study by Di Lenola et al. (52). These authors measured in migraine patients between attacks the effect of one 20-min session with Cefaly® on high frequency oscillations (HFO) embedded in somato-sensory evoked cortical potentials, which reflect thalamo-cortical activity and are decreased in migraine, indicating thalamo-cortical dysrhythmia (53). After eTNS, they found a significant increase in HFO. It remains to be determined if there is a relation between this finding and the eTNS-induced changes in activity of medial frontal cortex areas.

Conclusion

Taken together, the above described studies suggest that eTNS with the Cefaly® exerts its preventive anti-migraine action chiefly at supra-segmental levels, i.a. by modulating activity of medial frontal cortex areas involved in the control of the affective and cognitive dimensions of pain. These areas play indeed a paramount role in individual levels of central pain modulation in healthy subjects (54) and are dysfunctioning in chronic migraine (49), medication overuse headache (55) and chronic cluster headache (48). They are modulated both by transcutaneous and percutaneous pericranial nerve stimulation. The fact that involvement of medial frontal cortex areas seems not specific to migraine, nor limited to pain, and that eTNS can change thalamo-cortical circuits, may explain why pericranial neurostimulation, including eTNS, was reported to have also therapeutic effects in tension-type headache (56), fibromyalgia (57), depression (58) and epilepsy (59).

Regarding the acute effects of eTNS during a migraine attack, the mechanism of action might be different. The preventive eTNS effect on migraine takes time and becomes maximal after 3 months in the PREMICE trial (24), which is compatible with slow modulation of central pain control centres. By contrast, the acute analgesic effect of Cefaly® (30) and its inhibitory action on the nociceptive blink reflex during attacks (28) peak at 1h and tend to decrease thereafter, suggesting a transient inhibition of trigeminal nociception at the segmental level.

The predominant mode and site of Cefaly®'s action could thus differ between its acute effects, possibly exerted segmentally via somatic afferent-induced blockade of nociceptive trigeminovascular afferents, and its preventive effects, probably depending on activation of cortical areas controlling pain and its emotional aspects. Interestingly, the two mechanisms are intermingled in most Cefaly®-treated migraine patients, as they tend to use it both for prevention and for attack treatment.

Conflict of interest

Jean Schoenen is a consultant for Cefaly Technology.

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