Scientific advances in headache research: an update on neurostimulation


Jan Hoffmann*1 and Delphine Magis2

1Department of Neurology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
2Headache Research Unit, Department of Neurology, University of Liège, Boulevard du 12ème de Ligne 1, 4000 Liège, Belgium
* Author for correspondence: Tel.: +49 30 450 560 276 Fax: +49 30 450 560 912 jan.hoffmann@charite.de

3rd European Headache and Migraine Trust International Congress
London, UK, 20–23 September 2012

The pathophysiological understanding of migraine and other primary headaches has been substantially improved over the last 20 years. A milestone that paved the way for successful research was the development of the International Classification of Headache Disorders published by the International Headache Society in 1988. The classification facilitated a clear clinical diagnosis of headache disorders and allowed research efforts to be focused on clearly defined syndromes. Recent advances in the understanding of headache disorders have been driven by the availability of new research tools, such as advanced imaging techniques, genetic tools, pharmaceutical compounds and devices for electrical or magnetic stimulation. The latest scientific and clinical advances were presented at the recent European Headache and Migraine Trust International Congress (EHMTIC) in London (UK).

Neurostimulation is of increasing interest for the treatment of primary headaches. Initial experiences with invasive methods, such as deep brain stimulation for drug-refractory cluster headache, have been effective but were hampered by severe side effects. Research efforts are now being focused on noninvasive or minimally invasive neurostimulation therapies that could be used in less disabled patients. A variety of neurostimulation devices and first data about their potential efficacy were presented at the conference and are reviewed here.

Noninvasive neurostimulation devices
Transcranial magnetic stimulation
Transcranial magnetic stimulation (TMS) is an established method to modulate cortical excitability and has been used for several neurological purposes for many years. Holland et al. demonstrated in an in vivo model of migraine, that single-pulse TMS (sTMS) was able to inhibit
cortical spreading depression [1]. A recent randomized controlled trial (RCT) suggested a positive, although modest effect of sTMS for the acute treatment of migraine with aura [2]. At this year’s EHMTIC, sTMS was presented in the context of a postmarket pilot program of the SpringTMS™ device for the acute treatment of migraine [3]. In this study, 37 patients (24 migraine with aura, and 13 migraine without aura) used the device in an outpatient setting over three consecutive months. A total of 504 attacks of migraine with aura and 273 attacks of migraine without aura were treated. A significant reduction or alleviation of migraine pain was reported by 73% of the patients, while an improvement of migraine-associated symptoms was reported by 63%. No adverse events were reported. Taken together with the previous sTMS RCT, these results indicate that sTMS could be a promising acute migraine treatment. However the sample size was small and objective data from headache diaries are lacking. Further well-conducted RCTs and pharmacoeconomic data are warranted. In his invited new scientist lecture, A Vigano (Sapienza University of Rome, Rome, Italy) explained that excitatory intermittent theta burst repetitive pulse TMS (tTMS) of the visual cortex (i-TBS) applied to healthy volunteers could induce changes in cortical responsiveness, which should be able to normalize the cortical interictal neuronal abnormalities found in migraineurs, and so become a valuable migraine preventive treatment [4]. Clinical results of i-TBS in episodic migraineurs are eagerly awaited.

Transcranial direct current stimulation
Besides TMS, transcranial direct current stimulation (tDCS) is another central neuromodulatory technique that is able to modify neuronal firing, but previous trials performed in migraine disclosed inconsistent results [5]. Vigano presented the preliminary results of a proof-of-concept trial of excitatory anodal tDCS of the visual cortex performed in seven episodic migraineurs as preventive treatment [6]. After 2 months of treatment with anodal tDCS, there was an average significant reduction in migraine frequency (-36.65%) and attack duration (-43.25%), and the interictal habituation of visual evoked potentials tended to increase. Larger RCTs with anodal tDCS may thus be worthwhile in migraine.

Transcutaneous vagus nerve stimulation
Magis and Jean Schoenen (University of Liège) presented data about their initial experience with a transcutaneous vagus nerve stimulation (tVNS) device (Gammacore®). Twelve migraine without aura (five patients with medication-overuse headache), four trigeminal autonomic cephalalgia (TAC) and two hemicrania continua (HC) patients were included. Neurostimulation was performed three times daily over 90 s as preventive therapy. At the time of presentation, results were available for 13 patients. Out of these, ten patients had stopped the treatment before completion of the study due to lack of efficacy and/or significant side effects. A total of three patients (one medication overdose headache, one TAC and one HC) experienced a significant reduction in attack frequency, in two of them the benefit remained after 7-month follow-up [7]. In another trial, Nesbitt et al. used tVNS to treat 14 patients suffering from cluster headache (CH; seven chronic CHs and seven episodic CHs) during a median period of 13 weeks. Mean subjective improvement was 60% in 13 patients. Twelve patients were able to reduce or even stop their previous preventive treatment. The same authors also used rVNS to relieve pain in two HC patients previously treated with ONS [8]. Taken together, these results indicate that more trials are needed to clarify a potential efficacy of tVNS and that treatment of TACs could be a valuable indication.

Transcutaneous supraorbital stimulation
Case reports using invasive supraorbital stimulation have shown promising results [5]. Along the same line, the efficacy and safety of a transcutaneous supraorbital nerve stimulator (tSNS), the Cefaly® device, has been tested in a multicenter, double-blind, randomized, sham-controlled trial in 67 episodic migraineurs [9]. Patients were randomly assigned to verum or sham stimulation after a 1-month run-in period. tSNS was performed daily for 20 min during 3 months. The authors observed a significant reduction of monthly migraine days and attacks (both p = 0.04) and acute antimigraine drug intake (p = 0.007). The 50% responder rate was significantly higher in the verum (38.1%) than in the sham group (12.1%). There were no adverse events. These results suggest that tSNS with the Cefaly device might offer a promising alternative to drugs for the preventive treatment of migraine. Hence, if its effectiveness is slightly lower than the best pharmacologic prophylactic treatment, such as topiramate, the absence of adverse events constitutes a real advantage.

Invasive neurostimulation devices
Sphenopalatine ganglion neurostimulation
Schoenen presented the final results of the multicenter European Pathway CH-1 RCT on the efficacy of sphenopalatine ganglion stimulation (SPGS) for the treatment of chronic CH, using the ATIS® implantable microstimulator [10]. The preliminary results reported at the annual meeting of the American Academy of Neurology indicated that SPGS induced a significant reduction of frequency and intensity of CH [11]. The SPGS ATI device is surgically implanted into the pterygopalatine fossa and it electrically stimulates the sphenopalatine ganglion to disrupt the trigeminal parasympathetic reflex that involves the sphenopalatine ganglion. Stimulation is triggered by the patient using a handheld remote control. Available data suggest that this microstimulator is MR-safe. The blinded experimental period of the CH-1 trial was completed by 27 patients. Pain relief was achieved in 67% of headache attacks with full stimulation versus 8% for placebo. Twenty-six percent of patients experienced a significant pain relief in ≥50% of the attacks, 37% reported a frequency improvement of at least 50% and 7% had both effects. As a result of the surgical procedure 47% of the patients experienced transient and mild-to-moderate numbness in the second branch of the trigeminal nerve.

Occipital nerve stimulation
Several open trials have recently suggested that ONS could be effective in the prevention of drug-resistant chronic CH [12–16] and, to a lesser extent, chronic migraine [17–19].
During the conference J Vesper et al. (Heinrich–Heine University Hospital, Düsseldorf, Germany) presented a study in which they investigated the outcome of 20 patients with various therapy-refractory chronic headaches under ONS. Nine patients suffered from chronic migraine, one patient had a thalamic infarction, one CH, four tension type headache and five recurrent cervicogenic headache. Patients were followed up over 3 months. A total of 16 out of the 20 patients experienced a significant reduction in pain intensity. No adverse events were reported. This study on a variety of refractory headache types well illustrates that the mechanism of action of ONS in headache is absolutely nonspecific and does not act on the disease generator, as suggested before [15,20].

Conclusion
The high amount of neurostimulation trials and case reports presented at the 3rd EHMTIC contrasts with the obvious lack of new specific drugs in the headache field. Hence, no acute migraine-specific drugs have been released since the advent of triptans 20 years ago, and the hopes raised by gepants (CGRP antagonists), ditas (5HT1F agonists) and the CSD-blocker tonabersat are somewhat disappointing. Central neuromodulation techniques such as TMS or tDCS could become the first migraine-specific preventive therapies, as all preventive drugs used up to now are not specific to the disease. Even if the preliminary results obtained with minimally and noninvasive neurostimulation therapies in headache are promising, large well-conducted RCTs are missing for most devices and optimal device settings and mode of action are unknown.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

References