Review Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2016, Vol. 36(12) 1103–1111

DOI: 10.1177/0333102415620908
cep.sagepub.com

SAGE

Pathophysiological targets for non-pharmacological treatment of migraine

Gianluca Coppola[1], Cherubino Di Lorenzo[2], Mariano Serrao[3], Vincenzo Parisi[1], Jean Schoenen[4] and Francesco Pierelli[3,5]

Abstract

Background: Migraine is the most prevalent neurological disorder worldwide and ranked sixth among all diseases in years lived with disability. Overall preventive anti-migraine therapies have an effect in one patient out of two at the most, many of them being endowed with disabling adverse effects. No new disease-modifying drugs have come into clinical practice since the application to migraine of topiramate and botulinum toxin, the latter for its chronic form. There is thus clearly a need for more effective treatments that are devoid of, or have acceptable side effects. In recent years, scientific progress in migraine research has led to substantial changes in our understanding of the pathophysiology of migraine and paved the way for novel non-drug pathophysiological-targeted treatment strategies.

Overview: Several such non-drug therapies have been tested in migraine, such as oxidative phosphorylation enhancers, diets and non-invasive central or peripheral neurostimulation. All of them are promising for preventive migraine treatment and are quasi-devoid of side effects. Their advantage is that they can in theory be selected for individual patients according to their pathophysiological profile and they can (and probably should) be combined with the classical pharmacological armamentarium.

Conclusion: We will review here how knowledge of the functional anatomy and physiology of migraine mechanisms holds the key for more specific and effective non-pharmacological treatments.

Keywords

Non-pharmacological treatment, migraine pathophysiology, neurostimulation, nutraceuticals, diets

Date received: 20 June 2015; revised: 21 October 2015; accepted: 14 November 2015

Introduction

Migraine is the most prevalent neurological disorder worldwide and ranked sixth in the most disabling diseases affecting mankind. There are major problems for clinicians in treating migraine with the available preventive therapies. Firstly, the average efficacy rate of any prophylactic agent does not exceed 50%, and secondly, almost all prophylactic drugs are associated with cumbersome and sometimes intolerable adverse effects. Moreover, episodic migraine may evolve into a chronic form (>15 days/month with headache) that often becomes resistant to treatment, which heavily impacts on the patients' quality of life. It is fortunate therefore that numerous non-pharmacological treatments for migraine have been tested in recent years. They include the so-called nutraceuticals (riboflavin, coenzyme Q10 (CoQ10), magnesium, etc.), dietary interventions (low calorie, vegan, ketogenic, etc.) and peripheral nerve or transcranial neurostimulation. Many of these therapies still lack evidence-based data from large, randomized, placebo-controlled trials and are thus not

[1]G.B. Bietti Foundation IRCCS, Department of Neurophysiology of Vision and Neurophthalmology, Italy
[2]Don Carlo Gnocchi Onlus Foundation, Italy
[3]"Sapienza" University of Rome Polo Pontino, Department of Medico-Surgical Sciences and Biotechnologies, Italy
[4]Liège University, Headache Research Unit. University Department of Neurology, Belgium
[5]IRCCS Neuromed, Pozzilli (IS), Italy

Corresponding author:
Gianluca Coppola, Department of Neurophysiology of Vision and Neurophthalmology, G.B. Bietti Foundation-IRCCS, Via Livenza 3 – 00198, Rome, Italy.
Email: gianluca.coppola@gmail.com

widely used or accepted. The available clinical data are presented in other articles of this special issue (see (1–3)).

Dietary interventions

Inflammation is a potential unifying factor that may explain the link between diet and migraine. In fact, all factors implicated in the diet–migraine relationship may share inflammation as a common target. Levels of inflammatory cytokines are higher in obese subjects (4) and are normalized by weight loss, together with leukocyte counts and oxidative stress (5,6). Altered insulin metabolism in migraineurs may be related to adipocytokines (7) and nitric oxide stress (8), both of which promote inflammation. Adipocytokines are adipocyte-derived cytokines involved in energy homeostasis, obesity and diabetes. In particular, two subtypes of adipocytokines – leptin and adiponectin – could be involved in migraine pathophysiology. Leptin, which also has vasoactive and inflammatory properties, is higher in hyperinsulinemic migraineurs (9). High-molecular-weight adiponectin has been shown to induce inflammatory cytokine secretion and is related to chronic migraine (7,10). Interestingly, the flunarizine and amitriptyline-induced side effect of becoming overweight may be related to pharmacological induction of higher levels of insulin, leptin and C-peptide (11). Higher levels of insulin and leptin could in turn counteract treatment efficacy, and long-term use might worsen pre-existing migraine.

Several specific diets are proposed as effective strategies for improving migraine: low-sodium diet (12), deprivation diet (13), vegan diet (14) and ketogenic diet (KD) (15,16). The KD is particularly noteworthy with respect to migraine treatment. Classically, KD is regarded as a high-fat, low-carbohydrate diet that promotes ketone body (KB) production as an energetic substitute for glucose. It was adopted in the 1920s to treat drug-resistant epilepsy (17) and migraine (18). Over recent years, an alternative KD regimen, called very-low-calorie KD (VLCKD), which mimics fasting by restricting carbohydrates and fats, was proposed to achieve rapid weight loss. There are several aspects of VLCKD that could have beneficial effects on overweight migraineurs (15,16). KBs in this scenario may act on migraine through several mechanisms of action: firstly, modulating neuronal excitability (17); secondly, tapering neural inflammation (19); and thirdly, enhancing mitochondrial energetic metabolism (16). Available clinical trials of diets for migraine are reviewed elsewhere in this special issue of *Cephalalgia* (see (1)).

Nutraceuticals

The rationale for using high-dose nutraceutical supplements, such as riboflavin, CoQ10 and magnesium, in migraine prophylaxis comes from phosphorus-31 magnetic resonance (MR) spectroscopy studies showing that an unstable state of brain metabolism may be present in migraine patients. In fact, mitochondrial oxidative phosphorylation (OXPHOS; i.e. the energy reserve) is reduced by 25–30% interictally in the brains of migraineurs with or without aura (20,21). Mitochondria produce free radicals through OXPHOS and adenosine triphosphate. On the other hand, mutations in mitochondrial DNA (mtDNA) were reported in migraine associated with stroke episodes (22), and increased numbers of sequence variants were detected in the non-coding control regions of mtDNA in migraineurs with occipital stroke (23). Two single-nucleotide polymorphisms in the non-coding mtDNA were found to be more prevalent in children with migraine and cyclic vomiting (24), and migraine is highly prevalent in carriers of the mtDNA 3243A>G (MELAS) mutation (25).

Large doses of riboflavin (400 mg/day), like those given to patients with MELAS or mitochondrial myopathies, are assumed to increase activity of mitochondrial complexes 1 and 2, thereby improving clinical and biochemical abnormalities (26). CoQ10 is an essential cofactor of the electron transport chain in mitochondria (27). Administration of CoQ10 also increased complex-1 activity in a mouse model of Parkinson's disease (28). Mg^{2+} is the foremost regulator of metabolism, largely through its role as a cofactor for all phosphoryl transfers in the cell (29). Low brain magnesium levels have been detected using *in vivo* phosphorus-31 MR spectroscopy during (30) and between (31) migraine attacks, and low magnesium levels were also found in various other biological tissues (32,33). Impaired OXPHOS performance was the rationale for the use of OXPHOS enhancers (riboflavin, CoQ10, Mg) as prophylactic therapies in migraine. Available clinical trials of OXPHOS enhancers in migraine are reviewed elsewhere (1).

Neuromodulation

Transcranial magnetic stimulation and transcranial direct current stimulation

The rationale for the use of non-invasive neuromodulatory techniques comes from evidence that abnormal cortico-thalamic information processing characterizes the brains of migraine patients and that transcranial

magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are able to either activate or inhibit the underlying cerebral cortex. The abnormal information processing is characterized between attacks by a normal-to-low amplitude response to low numbers of stimuli, followed by an amplitude increase during prolonged stimulation (i.e. potentiation), contrasting with an amplitude decrease (i.e. habituation) in normal subjects. This has been observed for cortical responses to all sensory modalities, with the exception of olfaction. Abnormal cortical responsivity was also detected with power mapping of the resting electroencephalogram (EEG) as decreased alpha but increased theta power, and EEG hypersynchronization during repetitive photic stimulation (34). Abnormal rhythmic activity between the thalamus and cortex, namely thalamocortical dysrhythmia, which decrease preactivation levels of sensory cortices, may be the underlying pathophysiological mechanism for the habituation deficit in migraine (see (35) for a review).

In migraine patients, activation of the visual or sensorimotor cortices with high-frequency repetitive TMS (rTMS) was able to increase both the amplitude of the first visual (VEP) and somatosensory evoked responses and habituation over successive blocks of responses for several hours. By contrast, inhibiting low-frequency rTMS had negligible effects (36,37). Moreover, activating the sensorimotor cortex with rTMS was also able to increase the interictal low thalamo-cortical drive in migraine (37,38). Similarly, cortico-striato-thalamocortical functional network activity increased in controls after anodal tDCS over M1, but not after cathodal or sham tDCS (39). Five consecutive daily sessions of activating rTMS over the visual cortex of migraineurs increased VEP habituation for long periods, lasting up to a few days (40). In accordance with these rTMS studies, Viganò et al. (41) reported in migraine patients and controls that VEP habituation increased immediately after an activating anodal tDCS over the visual area. Anodal tDCS also decreased magnetophosphene thresholds in patients and controls, while cathodal tDCS increased these thresholds in healthy subjects, but not significantly so in migraine patients (42).

In animal models, single-pulse TMS was reported to be effective (43) or ineffective (44) for inhibiting cortical spreading depression (CSD) occurrence. Anodal tDCS was able to significantly modify the propagation velocity of CSD (45), especially when the underlying cortex was previously inhibited (46).

Taken together, the accruing knowledge about cortical responsivity and the cyclic functional and structural changes occurring in certain cerebral networks in migraine, combined with the technological advances in neuromodulation device development and the data showing their effects on brain activity, paved the way for clinical trials of transcranial neurostimulation methods for the acute and preventive treatment of migraine.

Peripheral (cranial) nerve stimulations

The Aδ and C fibers of the trigeminovascular system that innervates the meninges and is thought to be responsible for the headache in migraine converge in the spinal trigeminal nucleus, with similar nociceptive fibers coming from the somatic portion of the ophthalmic nerve and the greater occipital nerve (47). There is thus *a priori* an anatomical rationale for applying neurostimulation to somatic branches of the ophthalmic division of the trigeminal nerve and/or of the C2 dermatoma, with the objective of modifying the activity of trigeminovascular nociceptors in the spinal trigeminal nucleus. Electrophysiological and imaging studies have indeed shown functional changes of the trigeminal nociceptive system over the migraine cycle. In a functional MR imaging (MRI) study of the response to nociceptive stimuli of the nasal mucosa, the blood oxygen level-dependent signal in the spinal trigeminal nucleus increased with closer vicinity to the next attack (48). The blink reflex (BR), which is highly sensitive to changes in trigeminal activity, lacks habituation in migraineurs between attacks (49–51), but its recovery curve is normal (52), indicating absence of sensitization. During migraine attacks, sensitization and reduced pain thresholds were observed on the affected side compared to the non-affected side after noxious radiant CO_2 laser stimulation in the face (53) and with the nociception-specific BR (54).

The precise mechanism of action in migraine of peripheral neurostimulation methods still needs to be further studied. Nevertheless, some hints about possible mechanisms come from the known anatomical–functional organization of the trigeminovascular system and from some imaging studies in treated patients. Electrical stimulation of somatic branches of the ophthalmic nerve or of the greater occipital nerve activates large Aβ, whose collaterals could inhibit second-order nociceptors in the spinal trigeminal nucleus via a ''gate control'' mechanism. It also stimulates some Aδ fibers that converge on the same nucleus with visceral meningeal trigeminovascular afferents and could induce a phenomenon of ''after-suppression'' in trigeminal nociceptors (i.e. suppression of nerve cells firing after a period of prolonged stimulation) (55). Imaging studies in chronic migraine (56) and cluster headache patients (57) stimulated with a percutaneously implanted suboccipital stimulator, however,

show that peripheral neurostimulation modulates central areas involved in pain control, which might be responsible for its therapeutic effect. Overall, these clinical, structural and functional data have paved the way for targeting cranial nerves with neuromodulatory techniques.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) with implanted electrodes wrapped around its cervical portion is effective as an add-on treatment in medically intractable epilepsy and major depression. Several experimental studies in animals and observational reports in humans have also provided a rationale for using VNS in migraine therapy. The visceral afferent fibers that are the main fiber population of the vagus nerve in the neck project via the nucleus of the solitary tract to various central nervous system (CNS) centers that are known to be involved in migraine pathophysiology, such as the thalamus (58,59), the brainstem monoaminergic nuclei (60) and the limbic and somatosensory cortices (61). In freely moving cats, VNS with implanted electrodes had transient effects on neuronal activity in primary visual areas, causing a delay in the establishment of visual habituation (62), a phenomenon that is known to be dysfunctional in migraine between attacks (35). Moreover, VNS can modulate nociception, for instance by increasing pain thresholds (63), by reducing accruing pain associated with trains of consecutive stimuli (''wind-up'') (64) and also by modulating neuronal activity in the spinal trigeminal nucleus (65). The direction of the VNS-related effects on nociception induced by stimulation of the transected vagus nerve in animals depends, however, on the stimulation protocol. Overall, these experimental studies suggest that the anti-nociceptive effect of VNS might rely on central inhibition of pain rather than modifications of peripheral nociceptive mechanisms.

Several case reports have shown that VNS with the implantable cervical stimulation system can improve comorbid migraine in patients treated for intractable epilepsy (66–69). Invasive VNS was also reported to be effective in some chronic migraine patients (70,71).

The available clinical trials of TMS, tDCS and peripheral nerve stimulators in migraine are reviewed elsewhere (3).

Cognitive–behavioral therapy and neurofeedback

Migraine is commonly regarded as a bio-behavioral disorder resulting from a combination of behavioral and biological (CNS dysfunction) factors. The behavioral factors refer to actions or reactions of the individual in response to certain internal or external stimuli, such as stress. Repeated abnormal or excessive reactions can cause or worsen the disorder. As mentioned above, the migraineur's brain hyper-reacts to prolonged repeated stimuli, whatever its sensory modality. It also does this during cognitive tasks (see (35) for a review). That the altered information processing in migraine between attacks is associated with limbic system dysfunction is illustrated by several functional MRI studies. They showed, for example, interictal abnormalities in the functional resting state of affective pain regions that belong to multisensory–discriminative, cognitive/executive and integrative domains (72–74), strengthening the view that migraine is a bio-behavioral disorder.

Behavioral therapies aim at changing specific actions and use techniques to reduce or eliminate behaviors that create discomfort and to increase or acquire behaviors that promote a better quality of life (see Andrasik in this issue). Besides classical cognitive–behavioral therapies that are useful in migraine, particularly when associated with preventive drug therapy (75), the behavioral paradigm can be used to change and control measurable brain activities, which is a method that is called ''neurofeedback'' (NFB). NFB combines behavioral techniques and neurophysiological recordings to teach the individual how to control various aspects of their own brain activity, such as spontaneous or evoked EEG, and to promote self-regulatory processes, such as cognitive performance, stress levels, emotional functioning and behavior (76). Although the underlying neural mechanisms of self-regulation are not fully understood, it was proposed that self-regulation of brain activity is based on neuroplasticity mechanisms promoting short- and long-term changes in the bioelectric activity (77) of several interconnected cerebral areas, including, for instance, subcortical regulatory structures (76,78,79) and various cortical networks, including executive, salient and attentive networks (80,81). Because several of the latter subcortico-cortical brain networks are known to be dysfunctional in migraine, there is a biological rationale for using NFB in migraine therapy.

Conclusion

Migraine is a complex bio-behavioral disorder associated with cycling abnormalities of the function and structure of the brain networks involved in information processing, limbic and pain control, but also with a deficient mitochondrial energy metabolism. Pathophysiological findings in migraine have identified a number of brain targets that are amenable to selective modification by nutraceuticals, diets, external neurostimulation or to more global changes in cortical

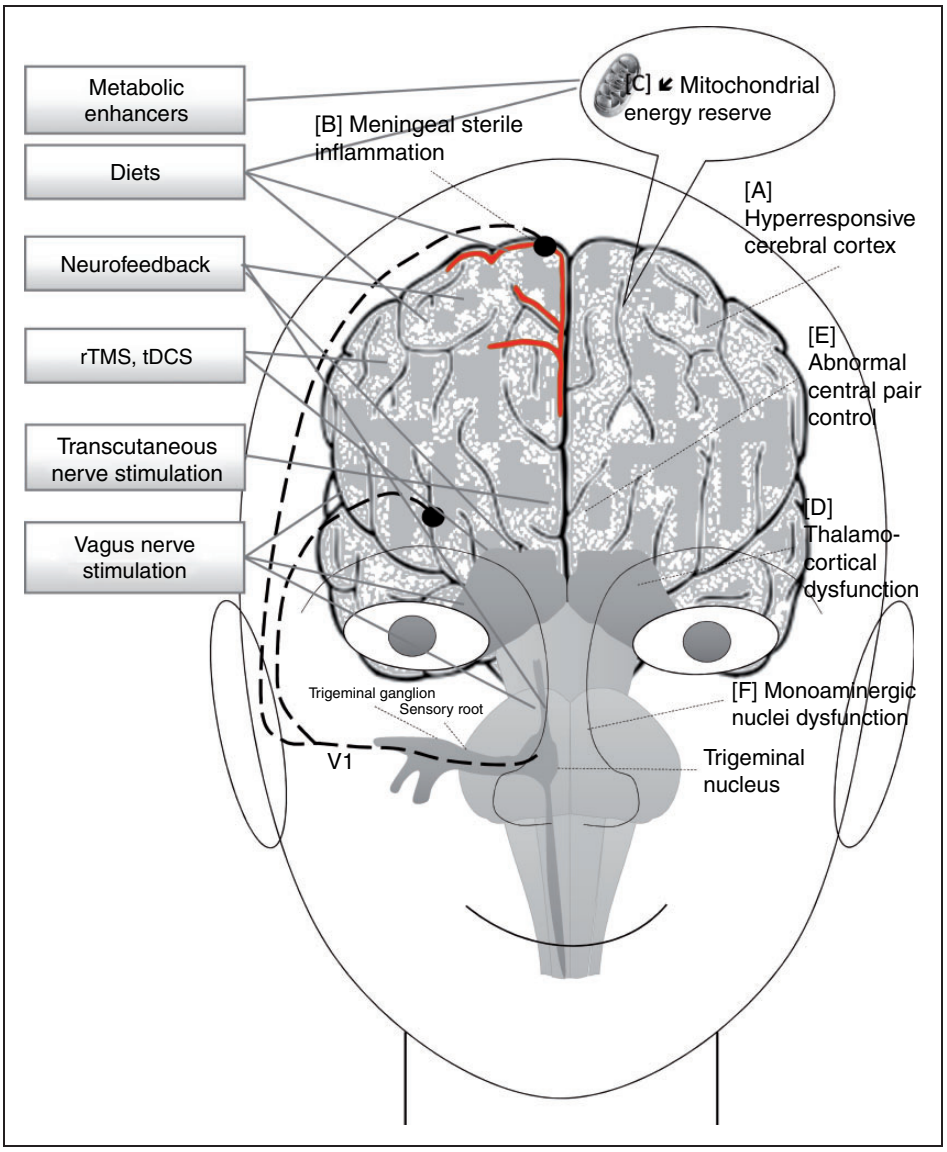

Figure 1. Scheme of migraine pathophysiological targets in migraine for non-pharmacological interventions. Diets could act by modulating neuronal excitability (a), mitigating sterile inflammation at the level of the trigeminovascular system (b) or enhancing mitochondrial energy metabolism (c). Nutraceuticals enhancing oxidative phosphorylation can augment the activity of mitochondrial complexes 1 and 2 (c). rTMS and tDCS are able to modify cortical responsivity (a) and thalamocortical circuits (d). Transcutaneous nerve stimulation may act by inducing long-term plasticity changes in central pain control centers (e). Vagus nerve stimulation is able to modulate the thalamus (d), the brainstem monoaminergic nuclei (f) and the cerebral cortex (a). Neurofeedback may act via neuroplastic changes in interconnected cerebral areas, such as the thalamus (d), brainstem (f) and various cortical networks (a), including executive, salient and attentional networks.
rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation.

networks by cognitive–behavioral and NFB therapy. They can be summarized as follows (see also Figure 1):

- Recent data indicate that, in subgroups of patients, migraine is related or at least correlated with the metabolic syndrome spectrum. The evidence for this is an association between obesity, insulin resistance and migraine. All of these pathologies are associated with a pro-inflammatory state. Different dietetic approaches have been tested to treat migraine and were found to be beneficial (Orr (1), this issue).
- Mitochondrial dysfunction resulting in impaired OXPHOS metabolism may play a role in migraine pathogenesis. Previous studies have proven the efficacy of OXPHOS enhancers such as riboflavin,

CoQ10 and magnesium in migraine prophylaxis. Whether the KD is suitable as a long-term strategy for migraine must be determined (see Orr (1), this issue).

- Lack of habituation at the trigeminal and cortical levels and low thalamocortical drive were demonstrated between attacks (35). Because these abnormalities can be partly reversed by the modern minimally invasive (2) or non-invasive neurostimulation techniques (see Schoenen et al. (3), this issue), many research groups have tested occipital nerve stimulation (ONS), rTMS, tDCS and transcutaneous nerve stimulation for migraine treatment, but with discrepant results and scarce sham-controlled trials.
- Migraine seems to be associated with interictal abnormal reactivity of spontaneous EEG and slow cognitive cortical potentials. This a rationale for the few studies that tested behavioral training programs such as NFB to treat migraine.

While all classical preventive anti-migraine drugs have multiple neurobiological effects and their sites of action in the pathophysiological cascade of migraine are uncertain, most of the non-pharmacological migraine therapies target one or a few of the facets of migraine pathophysiology, which may explain why their effect sizes are moderate overall. They have two major advantages, however. First, in future studies, they can (and should) be selected according to the pathophysiological phenotype of the individual patient, and second, because of their excellent tolerance and safety, most of them can be combined with a drug treatment or with another non-pharmacological therapy.

Clinical implications

- Although knowledge on migraine mechanisms has greatly increased in the last decade, there have been no significant advances in the marketed pharmacological treatment of the disorder.
- The available clinical data for alternative non-drug treatments are summarized in other articles of this special issue. Many of them still lack definitive evidence from placebo-controlled trials, but are able to target specific aspects of migraine pathophysiology.
- We review here the rationale for using nutraceuticals and neurostimulation methods in migraine therapy and illustrate how they open the perspective for treatment strategies customized to the pathophysiological profile of the individual migraine patient.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: the Italian Ministry of Health and Fondazione Roma financially supported the research for this paper.

References

1. Orr S. Diet and nutraceutical interventions for headache management: A review of the evidence. *Cephalalgia* 2015; doi:10.1177/0333102415590239.
2. Ambrosini A, D'Alessio C, Magis D and Schoenen J. Targeting pericranial nerve branches to treat migraine: Current approaches and perspectives. *Cephalalgia* 2015; 35: 1308–1322.
3. Schoenen J, Magis D and Coppola G. Non-invasive neurostimulation methods for migraine therapy: The available evidence. *Cephalalgia* 2015; in press.
4. Wisse B. The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004; 15: 2792–2800.
5. Chae J, Paik J, Kang R, et al. Mild weight loss reduces inflammatory cytokines, leukocyte count, and oxidative stress in overweight and moderately obese participants treated for 3 years with dietary modification. *Nutr Res* 2013; 33: 195–203.
6. Tajik N, Keshavarz S, Masoudkabir F, et al. Effect of diet-induced weight loss on inflammatory cytokines in obese women. *J Endocrinol Invest* 2013; 36: 211–215.
7. Peterlin B, Bigal M, Tepper S, Urakaze M, Sheftell F and Rapoport A. Migraine and adiponectin: Is there a connection? *Cephalalgia* 2007; 27: 435–446.
8. Gruber H, Bernecker C, Pailer S, et al. Hyperinsulinaemia in migraineurs is associated with nitric oxide stress. *Cephalalgia* 2010; 30: 593–598.
9. Bernecker C, Pailer S, Kieslinger P, et al. GLP-2 and leptin are associated with hyperinsulinemia in non-obese female migraineurs. *Cephalalgia* 2010; 30: 1366–1374.
10. Peterlin B, Alexander G, Tabby D and Reichenberger E. Oligomerization state-dependent elevations of adiponectin in chronic daily headache. *Neurology* 2008; 70: 1905–1911.
11. Berilgen M, Bulut S, Gonen M, Tekatas A, Dag E and Mungen B. Comparison of the effects of amitriptyline and flunarizine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment. *Cephalalgia* 2005; 25: 1048–1053.

12. Amer M, Woodward M and Appel L. Effects of dietary sodium and the DASH diet on the occurrence of headaches: results from randomised multicentre DASH-Sodium clinical trial. *BMJ Open* 2014; 4: 10.
13. Alpay K, Ertas M, Orhan E, Ustay D, Lieners C and Baykan B. Diet restriction in migraine, based on IgG against foods: a clinical double-blind, randomised, cross-over trial. *Cephalalgia* 2010; 30: 829–837.
14. Bunner A, Agarwal U, Gonzales J, Valente F and Barnard N. Nutrition intervention for migraine: A randomized crossover trial. *J Headache Pain* 2014; 15: 69.
15. Di Lorenzo C, Currà A, Sirianni G, et al. Diet transiently improves migraine in two twin sisters: Possible role of ketogenesis? *Funct Neurol* 2013; 28: 305–308.
16. Di Lorenzo C, Coppola G, Sirianni G, et al. Migraine improvement during short lasting ketogenesis: A proof-of-concept study. *Eur J Neurol* 2015; 22: 170–177.
17. Wheless J. History of the ketogenic diet. *Epilepsia* 2008; 8: 3–5.
18. Schnabel T. An experience with a ketogenic dietary in migraine. *Ann Intern Med* 1928; 2: 341–347.
19. Cullingford T. The ketogenic diet; fatty acids, fatty acid-activated receptors and neurological disorders. *Prostaglandins Leukot Essent Fatty Acids* 2004; 70: 253–264.
20. Barbiroli B, Montagna P, Cortelli P, et al. Abnormal brain and muscle energy metabolism shown by ^{31}P magnetic resonance spectroscopy in patients affected by migraine with aura. *Neurology* 1992; 42: 1209–1214.
21. Montagna P, Cortelli P and Barbiroli B. Magnetic resonance spectroscopy studies in migraine. *Cephalalgia* 1994; 14: 184–193.
22. Ojaimi J, Katsabanis S, Bower S, Quigley A and Byrne E. Mitochondrial DNA in stroke and migraine with aura. *Cerebrovasc Dis* 1998; 8: 102–106.
23. Majamaa K, Finnilä S, Turkka J and Hassinen I. Mitochondrial DNA haplogroup U as a risk factor for occipital stroke in migraine. *Lancet* 1998; 352: 455–456.
24. Zaki E, Freilinger T, Klopstock T, et al. Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. *Cephalalgia* 2009; 29: 719–728.
25. Guo S, Esserlind A, Andersson Z, et al. Prevalence of migraine in persons with the 3243A>G mutation in mitochondrial DNA. *Eur J Neurol* 2015; doi:10.1111/ene.12832.
26. Gerards M, van den Bosch BJ, Danhauser K, et al. Riboflavin-responsive oxidative phosphorylation complex I deficiency caused by defective ACAD9: New function for an old gene. *Brain* 2011; 134: 210–219.
27. Matthews R, Yang L, Browne S, Baik M and Beal M. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc Natl Acad Sci U S A*. 1998; 95: 8892–8897.
28. Sharma S, El Refaey H and Ebadi M. Complex-1 activity and ^{18}F-DOPA uptake in genetically engineered mouse model of Parkinson's disease and the neuroprotective role of coenzyme Q10. *Brain Res Bull* 2006; 70: 22–32.
29. Rubin H. The paradox of the contrasting roles of chronic magnesium deficiency in metabolic disorders and field cancerization. *Magnes Res* 2014; 27: 94–102.
30. Ramadan N, Halvorson H, Vande-Linde A, Levine S, Helpern J and Welch K. Low brain magnesium in migraine. *Headache* 1989; 29: 416–419.
31. Boska M, Welch K, Barker P, Nelson J and Schultz L. Contrasts in cortical magnesium, phospholipid and energy metabolism between migraine syndromes. *Neurology* 2002; 58: 1227–1233.
32. Schoenen J, Sianard-Gainko J and Lenaerts M. Blood magnesium levels in migraine. *Cephalalgia* 1991; 11: 97–99.
33. Sarchielli P, Coata G, Firenze C, Morucci P, Abbritti G and Gallai V. Serum and salivary magnesium levels in migraine and tension-type headache. Results in a group of adult patients. *Cephalalgia* 1992; 12: 21–27.
34. Coppola G and Schoenen J. Measures of cortical excitability. In: Borsook D, May A, Goadsby P and Hargreaves R (eds) *The Migraine Brain: Imaging Structure and Function*. New York: Oxford University Press, 2012, pp.321–338.
35. Coppola G, Di Lorenzo C, Schoenen J and Pierelli F. Habituation and sensitization in primary headaches. *J Headache Pain* 2013; 14: 65.
36. Bohotin V, Fumal A, Vandenheede M, et al. Effects of repetitive transcranial magnetic stimulation on visual evoked potentials in migraine. *Brain* 2002; 125: 912–922.
37. Coppola G, De Pasqua V, Pierelli F and Schoenen J. Effects of repetitive transcranial magnetic stimulation on somatosensory evoked potentials and high frequency oscillations in migraine. *Cephalalgia* 2012; 32: 700–709.
38. Coppola G, Vandenheede M, Di Clemente L, et al. Somatosensory evoked high-frequency oscillations reflecting thalamo-cortical activity are decreased in migraine patients between attacks. *Brain* 2005; 128: 98–103.
39. Polanía R, Paulus W and Nitsche M. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp* 2012; 33: 2499–2508.
40. Fumal A, Coppola G, Bohotin V, et al. Induction of long-lasting changes of visual cortex excitability by five daily sessions of repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers and migraine patients. *Cephalalgia* 2006; 26: 143–149.
41. Viganò A, D'Elia T, Sava S, et al. Transcranial direct current stimulation (tDCS) of the visual cortex: A proof-of-concept study based on interictal electrophysiological abnormalities in migraine. *J Headache Pain* 2013; 14: 23.
42. Chadaide Z, Arlt S, Antal A, Nitsche M, Lang N and Paulus W. Transcranial direct current stimulation reveals inhibitory deficiency in migraine. *Cephalalgia* 2007; 27: 833–839.
43. Holland P, Schembri C, Fredrick J and Goadsby P. Transcranial magnetic stimulation for the treatment of migraine aura? *Cephalalgia* 2009; 29: PO29.
44. Khodaie B, Saba V, Ahmadi M, Lotfinia A and Lotfinia M. Effect of transcranial magnetic stimulation on cellular

anatomy after repetitive cortical spreading depression. *Cephalalgia* 2015; 35: PO037.
45. Liebetanz D, Fregni F, Monte-Silva K, et al. After-effects of transcranial direct current stimulation (tDCS) on cortical spreading depression. *Neurosci Lett* 2006; 398: 85–90.
46. Fregni F, Liebetanz D, Monte-Silva K, et al. Effects of transcranial direct current stimulation coupled with repetitive electrical stimulation on cortical spreading depression. *Exp Neurol* 2007; 204: 462–466.
47. Kerr F. Central relationships of trigeminal and cervical primary afferents in the spinal cord and medulla. *Brain Res* 1972; 43: 561–572.
48. Stankewitz A, Aderjan D, Eippert F and May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *J Neurosci* 2011; 31: 1937–1943.
49. Katsarava Z, Giffin N, Diener HC and Kaube H. Abnormal habituation of 'nociceptive' blink reflex in migraine – evidence for increased excitability of trigeminal nociception. *Cephalalgia* 2003; 23: 814–819.
50. Di Clemente L, Coppola G, Magis D, Fumal A, De Pasqua V and Schoenen J. Nociceptive blink reflex and visual evoked potential habituations are correlated in migraine. *Headache* 2005; 45: 1388–1393.
51. Di Clemente L, Coppola G, Magis D, et al. Interictal habituation deficit of the nociceptive blink reflex: An endophenotypic marker for presymptomatic migraine? *Brain* 2007; 130: 765–770.
52. Coppola G, Di Clemente L, Fumal A, et al. Inhibition of the nociceptive R2 blink reflex after supraorbital or index finger stimulation is normal in migraine without aura between attacks. *Cephalalgia* 2007; 27: 803–808.
53. de Tommaso M, Guido M, Libro G, et al. Abnormal brain processing of cutaneous pain in migraine patients during the attack. *Neurosci Lett* 2002; 333: 29–32.
54. Kaube H, Katsarava Z, Przywara S, Drepper J, Ellrich J and Diener HC. Acute migraine headache: Possible sensitization of neurons in the spinal trigeminal nucleus? *Neurology* 2002; 58: 1234–1238.
55. Villanueva L and Noseda R. Trigeminal mechanisms of nociception. In: McMahon SB, Koltzenburg M, Tracey I and Turk DC (eds) *Wall and Melzack's Textbook of Pain*. Philadelphia: Elsevier Health Sciences, 2013, pp.793–802.
56. Matharu MS, Bartsch T, Ward N, Frackowiak RSJ, Weiner R and Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: A PET study. *Brain* 2004; 127: 220–230.
57. Magis D, Bruno M, Fumal A, et al. Central modulation in cluster headache patients treated with occipital nerve stimulation: An FDG-PET study. *BMC Neurol* 2011; 11: 25.
58. Chandler M, Zhang J and Foreman R. Vagal, sympathetic and somatic sensory inputs to upper cervical (C1–C3) spinothalamic tract neurons in monkeys. *J Neurophysiol* 1996; 76: 2555–2567.
59. Narayanan J, Watts R, Haddad N, Labar D, Li P and Filippi C. Cerebral activation during vagus nerve stimulation: a functional MR study. *Epilepsia* 2002; 43: 1509–1514.
60. Fornai F, Ruffoli R, Giorgi F and Paparelli A. The role of locus coeruleus in the antiepileptic activity induced by vagus nerve stimulation. *Eur J Neurosci* 2011; 33: 2169–2178.
61. Fernández-Guardiola A, Martínez A, Valdés-Cruz A, Magdaleno-Madrigal V, Martínez D and Fernández-Mas R. Vagus nerve prolonged stimulation in cats: Effects on epileptogenesis (amygdala electrical kindling): Behavioral and electrographic changes. *Epilepsia* 1999; 40: 822–829.
62. Martínez-Vargas D, Valdés-Cruz A, Magdaleno-Madrigal V, Almazán-Alvarado S and Fernández-Mas R. Effects of electrical stimulation of the vagus nerve on the development of visual habituation in the cat. *Behav Brain Res* 2009; 205: 45–49.
63. Randich A and Gebhart G. Vagal afferent modulation of nociception. *Brain Res Brain Res Rev* 1992; 17: 77–99.
64. Kirchner A, Birklein F, Stefan H and Handwerker H. Left vagus nerve stimulation suppresses experimentally induced pain. *Neurology* 2000; 55: 1167–1171.
65. Lyubashina O, Sokolov A and Panteleev S. Vagal afferent modulation of spinal trigeminal neuronal responses to dural electrical stimulation in rats. *Neuroscience* 2012; 222: 29–37.
66. Sadler R, Purdy R and Rahey S. Vagal nerve stimulation aborts migraine in patient with intractable epilepsy. *Cephalalgia* 2002; 22: 482–484.
67. Hord E, Evans M, Mueed S, Adamolekun B and Naritoku D. The effect of vagus nerve stimulation on migraines. *J Pain* 2003; 4: 530–534.
68. Lenaerts M, Oommen K, Couch J and Skaggs V. Can vagus nerve stimulation help migraine? *Cephalalgia* 2008; 28: 392–395.
69. Basic S, Sporis D, Chudy D, Grahovac G and Nevajda B. The effect of vagus nerve stimulation on migraine in patient with intractable epilepsy: Case report. *Neurol Sci* 2013; 34: 797–798.
70. Mauskop A. Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. *Cephalalgia* 2005; 25: 82–86.
71. Cecchini AP, Mea E, Tullo V, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. *Neurol Sci* 2009; 1: S101–S104.
72. Russo A, Tessitore A, Giordano A, et al. Executive resting-state network connectivity in migraine without aura. *Cephalalgia* 2012; 32: 1041–1048.
73. Schwedt T, Schlaggar B, Mar S, et al. Atypical resting-state functional connectivity of affective pain regions in chronic migraine. *Headache* 2013; 53: 737–751.
74. Coppola G, Di Renzo A, Tinelli E, et al. Evidence for brain morphometric changes during the migraine cycle: A magnetic resonance-based morphometry study. *Cephalalgia* 2015; 35: 783–791.
75. Holroyd K, Cottrell C, O'Donnell F, et al. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: Randomised controlled trial. *BMJ* 2010; 341: 10.
76. Ninaus M, Kober S, Witte M, Koschutnig K, Neuper C and Wood G. Brain volumetry and self-regulation of

brain activity relevant for neurofeedback. *Biol Psychol* 2015; 110: 126–133.
77. Gruzelier J. EEG-neurofeedback for optimising performance. I: A review of cognitive and affective outcome in healthy participants. *Neurosci Biobehav Rev* 2014; 44: 124–141.
78. Birbaumer N, Ruiz S and Sitaram R. Learned regulation of brain metabolism. *Trends Cogn Sci* 2013; 17: 295–302.
79. Sulzer J, Sitaram R, Blefari M, et al. Neurofeedback-mediated self-regulation of the dopaminergic midbrain. *Neuroimage* 2013; 83: 817–825.
80. Ros T, Théberge J, Frewen P, et al. Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. *Neuroimage* 2013; 65: 324–335.
81. Haller S, Kopel R, Jhooti P, et al. Dynamic reconfiguration of human brain functional networks through neurofeedback. *Neuroimage* 2013; 81: 243–252.