Chapter 47
Brain stimulation in migraine

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INTRODUCTION

Migraine is a very prevalent disease (about 12% in the general population) with a great individual disability and socioeconomic burden due to workday loss or reduced productivity (Lipton et al., 2007; Stovner et al., 2007). In about 25% of the cases migraine headache is preceded or associated with transitory neurological symptoms and/or signs (aura) due to temporary dysfunction of cerebral cortex or of brainstem, more frequently represented by visual disturbance. According to the presence or not of such symptoms, migraine is defined as migraine with aura (MwA) or migraine without aura (MwoA). In some patients, the aura could also involve the motor system, presenting with hemiparesis; this condition is in some cases inherited (with autosomal dominant pattern) and is defined as familial hemiplegic migraine (FHM) (Headache Classification Subcommittee of the International Headache Society, 2004).

Despite intensive research effort in the last 20 years, which has continually increased our knowledge about disease mechanisms leading also to advances in treatment options, the precise etiopathogenesis of migraine remains to be elucidated. Recently, much importance has been given to mechanisms underlying the cortical excitability that has been suggested to be dysfunctioning in migraine. This view was prompted particularly by the discovery, in different forms of FHM, of genetically mediated abnormalities affecting neuronal membrane structures that could play a critical role for cortical excitability: P/Q calcium channels in FHM1 (Ophoff et al., 1996), Na/K ATPase in FHM2 (De Fusco et al., 2003), and sodium channels in FHM3 (Dichgans et al., 2005). Further evidence about the role of cortical excitability in migraine was provided also by experimental studies in animals with knockin for the FHM1 gene (van den Maagdenberg et al., 2004, 2010; Tottene et al., 2009), and more recently also for FHM2 gene (Leo et al., 2011). These animals were shown to be more prone to the induction of cortical spreading depression (CSD), a phenomenon that is considered to be the pathophysiological basis of the migraine aura.

Neurophysiological techniques, because their ability to allow study of patients with migraine directly and noninvasively, have been employed largely to investigate the issue of cortical excitability in the pathophysiology of migraine (Schoenen et al., 2003; Ambrosini et al., 2010). Among these techniques there has been particular interest in evoked potentials (EPs) and electrophysiological procedures able to perform effective and noninvasive brain stimulation, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Moreover, TMS, repetitive TMS (rTMS), and tDCS, because of their ability to interfere with and/or modulate cortical activity inducing persistent, plastic effects, have also been explored as potential therapeutic approaches, opening interesting perspectives for noninvasive neurostimulation for both symptomatic and preventive treatment of migraine and other types of headache.

In this chapter we review evidence regarding the role of noninvasive brain stimulation in the pathophysiology and treatment of migraine, delineating the advantages and limits of these techniques together with potential developments and future applications.

PATHOPHYSIOLOGY OF MIGRAINE: THE NEUROSTIMULATION INSIGHT

Currently, CSD and trigeminovascular activation are generally considered the likely pathophysiological mechanisms underlying aura and migraine pain, respectively. The trigeminovascular system consists of trigeminal...
nerve endings on meningeal vessels, which become activated during the attack, releasing substance P, calcitonin gene-related peptide, and other substances that induce vasodilation and favor nociceptive neural transmission to the trigeminal nucleus caudalis and thereby produce pain (Goadsby, 2007).

First described by Leao (1944), CSD is a wave of intense depolarization followed by hyperpolarization and reduced neuronal activity that can be induced experimentally in animals through mechanical or chemical stimulation of cortex, and that moves slowly across the cortical mantle at a velocity of 2–3 mm per minute. Besides experimental evidence in animals, metabolic and neurophysiological changes compatible with CSD have been reported respectively in functional neuroimaging (Hadjikhani et al., 2001) and magnetoencephalographic (Bowyer et al., 2001) studies in patients with migraine during aura. On this basis, CSD is now considered the likely neurophysiological basis of the migraine aura (Lauritzen, 1994; Goadsby, 2007), and potentially also the first step for migraine pain, as experimental studies in animals have shown the ability of CSD to activate the trigeminovascular system (Bolay et al., 2002; Zhang et al., 2011).

As well as features of migraine pain and aura, the basic abnormalities that predispose to attack recurrence represent the more relevant aspect and are still to be elucidated. The most relevant factors involved are considered to be dysfunctions in cortical excitability and in the brainstem structures involved in pain processing and control.

Neurophysiological techniques: evoked potentials

Among neurophysiological techniques, EPs gave the first valuable insight into the pathophysiology of migraine, showing that habituation to repeated visual stimulations (expressed as a progressive amplitude reduction in subsequent blocks of averaged evoked responses) is abolished in migraine. First documented with visual evoked responses (Schoenen et al., 1995; Afra et al., 1998b), the lack of habituation has since been confirmed across all sensory modalities, in both MwA and MwoA, and is considered a neurophysiological hallmark of the disorder (Coppola et al., 2009). The interpretation of impaired habituation represented the basis for the theory of reduced activation of sensory cortices proposed by Schoenen (1996), depending on the principle of a “ceiling” of neural activation. According to this theory, healthy subjects who have normal preactivation of sensory cortex easily reach the top (“ceiling”) of response activity after repeated sensory stimulation and show habituation. In contrast, migraineurs, who start with a lower level of activation, have a large range for suprathreshold activation up to the ceiling, explaining the lack of habituation to repeated stimuli. Moreover, the reduced preactivation would also explain the reduced amplitude of mean evoked response of the early block that was found for multimodal EPs and also in brainstem reflexes (Coppola et al., 2009).

Evidence in support of such a hypothesis has been provided recently by more sophisticated EP techniques analyzing high-frequency oscillations (HFOs) of somatosensory (SEP) and visual (VEP) evoked potentials. Indeed, the early component of HFOs in SEPs (due to thalamocortical activation) is reduced and habituation of the late component of gamma-band oscillations (GBOs) in VEPs (that is expression of visual cortical activation) is impaired (Coppola et al., 2005, 2007a).

Interestingly, impaired habituation has also been found for nociceptive sensory inputs through the technique of laser evoked potentials (LEPs) in migraine, and LEPs showed also abnormal responses to capsaicin application and to distracting stimuli (de Tommaso, 2008). This, together with other neurophysiological evidence of abnormal nociceptive responses, further supports the role of dysfunction of nociceptive processing and control, together with abnormalities of cortical excitability in migraine.

Contribution of noninvasive brain stimulation

Further pathophysiological insight came from the application of the noninvasive brain stimulation techniques, TMS and tDCS. TMS is an easy technique for painless cerebral stimulation through application of a magnetic field on the scalp. If given in repeated pulses (rTMS) it can produce longlasting plastic effects that remain after the end of the train and depend on the stimulation frequency used: frequencies of 1 Hz or less (low-frequency rTMS, LF-rTMS) reduce, whereas frequencies above 1 Hz (high-frequency rTMS, HF-rTMS) increase cortical excitability. tDCS is based on direct current delivered transcranially through electrodes positioned on the scalp and is thought to exert its modulatory effects on cortical excitability, polarizing cell membranes with anodal currents inducing facilitatory effects and cathodal currents causing inhibitory effects (Wagner et al., 2007). These noninvasive brain stimulation techniques, in particular TMS and rTMS, have been employed largely to investigate pathophysiological mechanisms in migraine. Initially, single-pulse and double-pulse TMS techniques have been used to assess levels of cortical excitability, whereas rTMS and later tDCS have been employed further as modulatory techniques to evaluate cortical responsiveness and plasticity.
in patients with migraine. No unequivocal picture has emerged from these data, or from those obtained by other techniques (neuroradiological, neurochemical, psychophysical), and the characterization of cortical dysfunction in migraine remains an unsolved issue. Most authors have found data supporting cortical hyperexcitability due to glutamatergic dysfunction (Aurora and Wilkinson, 2007; Vikelis and Mitsikostas, 2007) or impaired inhibitory processes of cortical circuitry (Brighina et al., 2009). In contrast, neurophysiological findings by other authors have been explained as due to decreased thalamocortical activity leading to cortical hypoexcitability (Coppola et al., 2007b). More recent data seem to highlight the relevance of homeostatic plasticity mechanisms in interpreting the neurostimulation findings in migraine.

In the following sections, we review in more detail the contribution of neurostimulation techniques to the understanding of migraine pathophysiology. We first discuss TMS studies on visual and motor cortex, and then the evidence from rTMS and tDCS as neuromodulatory techniques used to evaluate pathophysiological hypotheses with a particular focus on homeostatic plasticity. We also discuss more specific issues concerning the contribution of neurostimulation techniques in the study of the migraine cycle, in the transformation from episodic to chronic migraine (called chronicification), and in evaluating the effects of migraine-preventive drugs on cortical excitability and their relation with clinical outcome.

**Excitability of visual cortex in migraine**

In 1998, Aurora and colleagues employed single-pulse TMS to explore the excitability of the visual cortex in patients affected by MwA, through measurement of the phosphene threshold (PT), defined as the minimal intensity of magnetic pulse over occipital cortex able to induce perception of phosphenes. They found that patients perceived phosphenes more easily and had lower PT values than controls, thereby offering the first direct neurophysiological correlate of hyperexcitability of the occipital cortex in migraine. Similar results with the same technique (increased excitability of primary visual cortex) were reported also by others (Mulleners et al., 2001a; Aurora et al., 2003; Gerwig et al., 2005; Gunaydin et al., 2006). Evidence of cortical hyperexcitability has also been provided for the extrastriate cortex V5 (an area specifically involved in visual perception of motion). Indeed, Battelli and coworkers (2002) showed a reduced threshold for the induction of “moving phosphenes” (particular phosphenes that are perceived to move in the visual field) in migraineurs. However, opposite results were reported by Afra et al. (1998a) using a circular coil, and later also by Bohotin et al. (2003) using a focal coil, which showed a lower prevalence of phosphenes in patients with respect to controls. Partly in agreement with these results is also the paper by Lo and colleagues (2008), who reported an inverse correlation between phosphene prevalence and migraine severity, demonstrating less ability to induce phosphenes in migraine patients with greater disability. Moreover, the reliability of phosphenes as a subjective measure was questioned, and Antal et al. (2006) found increased variability of the PT in patients affected by migraine with respect to healthy controls. To establish more objective and reliable measures for visual cortical excitability, Mulleners and coworkers (2001b) used the experimental paradigm, first introduced by Amassian et al. (1989), in which a timed-pulse TMS over visual cortex, delivered 80–120 ms after initiation of a visual stimulus, resulted in suppression of visual perception acuity, likely due to the activation of inhibitory circuits. Mulleners et al. (2001b) found that TMS interference (magnetic suppression of perceptual accuracy, MSPA) was reduced in patients with MwA, and interpreted these results as due to reduced activity of inhibitory circuits of visual cortex in migraine. In a further study, the procedure was also found to be highly reliable at test–retest in controls (Custers et al., 2005), and therefore adequate for repeated measures, to evaluate modulatory effects following cortical stimulation and/or pharmacological treatment. Using this technique, Aurora and colleagues (2005) found a significantly greater reduction of MSPA in chronic migraine compared with episodic migraine, thus providing a neurophysiological link between cortical dysfunction and the degree of clinical impairment. The authors considered chronic migraine as a condition at one end of the migraine disease spectrum and not as a separate entity (Aurora, 2009).

**Excitability of motor cortex in migraine**

As well as the visual domain, motor cortical activity has been explored in migraine to evaluate whether changes in cortical excitability extend to areas other than the visual cortex, and also to obtain more objective and quantifiable measures through the study of motor evoked potentials (MEPs). A widely used measure to evaluate excitability of motor cortex is the motor threshold (MT), which can be defined as the minimal intensity of motor cortex stimulation able to induce MEPs of at least 50 µV with 50% probability (Rossini et al., 1994). Neurophysiological study of motor cortex also offers the only objective, validated method to investigate activity of intracortical circuits with the paired-pulse paradigm (Kujirai et al., 1993). Here, a conditioning pulse given below the MT (to modulate cortex without activation of corticospinal pathway) is followed, at different interstimulus intervals (ISIs), by a suprathreshold test
stimulus; the activation of specific intracortical circuits depends on the ISI used: ISIs of 2–5 ms activate $\gamma$-aminobutyric acid type A (GABA$_{\gamma}$)-dependent inhibitory circuits (short-latency intracortical inhibition, SICI) and ISIs above 5 ms activate facilitatory circuits (intracortical facilitation, ICF). Another frequently used method for evaluation of cortical inhibition (more specifically dependent on GABA$_{\gamma}$ circuits) is represented by the cortical silent period (CSP), the interruption of voluntary muscle activity induced by TMS of motor cortex.

Initial papers exploring motor cortex excitability in migraine were those by Bettucci et al. (1992) and Maertens de Noordhout et al. (1992). The first team evaluated a group of patients affected by menstrual migraine with MT and central conduction time (the time interval between latencies of motor response obtained by cortical stimulation and that following cervical stimulation) both during attacks and interictically. They found significant higher MT values both during and between attacks in patients compared with controls. Similar results were also found by the second team in patients affected by MwA, where increased MT values were found ipsilateral to the side of somatosensory aura. Increased MT values in MwoA were also found by Afra et al. (1998a) using a circular coil, whereas only a trend toward higher MT values in MwA were found by the same group (Bohotin et al., 2003) with a focal coil. This, together with a reduced prevalence of phosphene perception found in the same studies, led the authors to suggest a condition of cortical hypoexcitability in migraine. In contrast, van der Kamp and coworkers (1996) found an increased ratio of MEP/compound motor action potential in patients with MwA, interpreting the result as expression of cortical hyperexcitability. Reduced MT and increased MEP recruitment (greater incremental MEP responses on single-pulse TMS with increasing stimulation intensity) were also reported by Khedr et al. (2006), in agreement with the view of cortical hyperexcitability. On the other hand, the study by Werhahn et al. (2000), and some years later that by Gunaydin et al. (2006), could not find any significant change in parameters of cortical excitability (MT, CSP, intracortical inhibition, and facilitation), and concluded that there was no relevant motor cortex involvement in migraine. However, in more recent studies changes in intracortical circuit activity were reported by Siniatchkin et al. (2007), who found increased intracortical facilitation in patients with MwoA, and by Brighina et al. (2005, 2010), who showed reduced activity of inhibitory circuits, as expressed by SICI measures in MwA. Further evidence in support of dysfunction of inhibitory circuits was also provided by Aurora et al. (1999), who found reduced CSP duration in patients affected by MwA. This was confirmed by Khedr and colleagues (2006) and Currà and coworkers (2007), who found a significant reduction in CSP of facial muscles, which depends solely on cortical inhibitory circuits. CSP reduction was not found in some other studies (Werhahn et al., 2000; Gunaydin et al., 2006). However, recently, CSP changes specifically correlating with medication overuse have been reported by Currà et al. (2011), who showed significantly decreased CSP in patients with chronic migraine who were abusing triptans (but not nonsteroidal anti-inflammatory drugs). These authors also found a correlation between drug consumption and CSP duration, establishing a more direct link between defective cortical inhibition and the degree of clinical impairment.

**Cortical modulation by rTMS and tDCS and pathophysiological hypotheses**

In 2002, Bohotin and colleagues first used rTMS to explore the effects of cortical modulation on habituation to VEPs in migraine. These authors hypothesized that if dishabituation depends on cortical hypoexcitability (as suggested by Schoenen, 1996), then HF-rTMS (which has facilitatory effects in normals) should be able to normalize habituation in migraineurs. On the other hand, LF-rTMS (which reduces cortical excitability) should disrupt habituation in healthy subjects. The results confirmed the authors’ expectations: in migraineurs, HF-rTMS restored habituation, which was in turn disrupted by LF-rTMS in controls (Fig. 47.1). This interpretation has been questioned, because the theoretical construct of the experiment depends on the effects of rTMS and these unfortunately can change greatly, depending on basal state of the stimulated cortex, giving rise to paradoxical responses in conditions of increased or decreased cortical excitability (Brighina and Fierro, 2007; Valeriani et al., 2007). Thus, a risk of circular reasoning occurs because the effects of rTMS are used directly to assess a variable, i.e., cortical excitability, that could itself affect rTMS results.

Indeed, using 1-Hz rTMS, which reduces cortical excitability in healthy subjects, we found a paradoxical facilitatory behavior in both striate (V1) and extrastriate (V2) visual cortices in MwA (Fig. 47.2): 1 Hz on V1 reduced PT values, whereas on V2 the same frequency obtained faster reaction times to illusory contours stimuli (perceptual work specifically processed by V2) (Brighina et al., 2002; Fierro et al., 2003). We confirmed similar effects in motor cortex, where 1-Hz rTMS determined activation of facilitatory circuits in migraine, as expressed by increased ICF (Brighina et al., 2005). We interpreted these results as being due to reduced efficiency of inhibitory circuits unable to be upregulated.
by 1-Hz rTMS. In the same study we found reduced SICI at baseline in patients, in agreement with evidence regarding the insufficiency of inhibitory circuits reported in migraine by several studies (for a review see Brighina et al., 2009); results in agreement with reduced inhibition were also found by a tDCS study on visual cortex where cathodal currents were unable significantly to increase PT values in patients with migraine (Chadaide et al., 2007). Concerning this matter, in analogy with the observation by Lefaucheur et al. (2006) in neuropathic pain, we found that HF-rTMS was able to normalize SICI in migraine, also favoring the recovery of the normal inhibitory response to 1-Hz rTMS (Brighina et al., 2010). This appears to be in line with studies by Bohotin et al. (2002) and Fumal et al. (2006), which obtained normalization of habituation in migrainers through HF-rTMS. On this basis, a relationship between habituation and cortical inhibition appeared suitable, allowing us to explain the modulatory effects of HF-rTMS. In a subsequent report we provided evidence

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**Fig. 47.1.** Effects of repetitive transcranial magnetic stimulation (rTMS) on habituation to visual evoked potentials (only significant changes are shown): (A) impaired habituation by 1-Hz rTMS in controls; (B) restored habituation by 10-Hz rTMS in patients with migraine with aura (MwA). (Modified from Bohotin et al., 2002.)

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**Fig. 47.2.** Paradoxical facilitatory responses to 1-Hz repetitive transcranial magnetic stimulation (rTMS) of (A) striate and (B) extrastriate visual cortex in patients with migraine with aura. Note the reduced phosphene threshold (PT) values (A) and lower reaction time (RT) to illusory contour stimuli in patients compared with increased PT and RT values in controls. (Parts (A) and (B) modified from Brighina et al., 2002, and Fierro et al., 2003, respectively.)
linking impaired habituation and reduced inhibition in an experimental model in which healthy subjects underwent visual deprivation, a procedure known to induce downregulation of GABA circuits (Boroojerdi et al., 2000, 2001; Fierro et al., 2005). Under these conditions, subjects behaved like migraineurs, showing impairment of habituation that recovered after treatment with HF-rTMS. Moreover, subjects showed a paradoxical response with further impairment of habituation and even potentiation of the VEP response with LF-rTMS (Palermo et al., 2011). Thus, it is conceivable that reduced inhibition could be the basis of impaired habituation in migraine, also explaining paradoxical responses to rTMS.

Reduced inhibition has been considered one mechanism underlying cortical hyperexcitability in migraine, but it could also result from a condition of general hypoactivity of cortical neurons secondary to dysfunctioning thalamocortical circuits (Coppola et al., 2007b). A critical point to disentangle between these two alternative explanations could be made by the assessment of activity and responsivity of facilitatory circuits. Recently, Conte et al. (2010) applied to the primary motor cortex brief trains of HF-rTMS, which are known to induce in healthy subjects a progressive MEP potentiation, likely due to presynaptic mechanisms of glutamatergic neurotransmission. The authors found a greater potentiation in migraineurs with respect to controls, providing evidence of hyperactive mechanisms of short-term plasticity in migraine. This gave further support to the involvement of a glutamate dysfunction in migraine pathophysiology according to the evidence previously provided by: (1) animal models of FHM, suggesting increased glutamate release as the final common effect of different genetic alterations (Pietrobon and Striessnig, 2003; van den Maagdenberg et al., 2004); (2) studies on patients showing increased interictal cerebrospinal and plasma glutamate levels (Alam et al., 1998; Peres et al., 2004); and (3) impaired glutamatergic metabolism in platelets (Vaccaro et al., 2007). Dysfunction of glutamate facilitatory circuits together with reduced GABAergic activity (Brighina et al., 2009) can both underlie abnormalities of cortical excitability in migraine, but the interactions between facilitatory and inhibitory intracortical circuits still remain to be elucidated. Indeed, it can be difficult to determine the real contribution of reduced inhibition and whether it is due to a primitive GABAergic dysfunction or to a failure of GABAergic interneurons in inhibiting hyperactive glutamatergic circuits. Concerning this point, recent studies have supported the idea that measures used widely to assess inhibition in human motor cortex such as SICI can be contaminated by intracortical facilitatory processes (Peurala et al., 2008). Thus, it cannot be excluded at all that evidence of reduced SICI may, at least in part, be due to increased activity of facilitatory circuits rather than reduction of the inhibitory ones.

Cortical modulation and mechanisms of homeostatic plasticity in migraine

Recently, using the same technique employed by Conte et al. (2010), we showed a different response pattern to 5-Hz rTMS trains in patients with MwA depending on the stimulation intensity used. At lower intensities that were unable to produce MEP potentiation in healthy subjects, we found MEP facilitation. Conversely, we observed paradoxical MEP inhibition at higher stimulation intensity (Brighina et al., 2011) (Fig. 47.3). Although the facilitation at low intensity, in analogy with the study by Conte et al. (2010), could be attributed to hyperresponsive mechanisms of glutamatergic neurotransmission, the inhibition observed at higher intensities appears more puzzling. To explain it we invoked a potential role of homeostatic plasticity mechanisms regulating presynaptic glutamate release. Homeostatic plasticity concerns mechanisms that stabilize neuronal excitability within a physiological dynamic range in the human motor cortex, avoiding excessive excitation and damage of neural systems (Bienenstock et al., 1982). These mechanisms have been explored recently in human studies in which
tDCS was employed to increase or decrease cortical excitability before the application of rTMS. Here, LF-rTMS (inhibitory) and HF-rTMS (facilitatory) even induced opposite effects, depending on the excitability level of the primary motor cortex previously changed by tDCS (Lang et al., 2004; Siebner et al., 2004). Thus, when 5-Hz rTMS was given after facilitatory anodal tDCS it induced inhibitory rather than facilitatory effects on MEPs.

In the light of these studies, the concept that a given paradigm of stimulation may have facilitatory or inhibitory effects on cortical excitability in each condition of stimulation has to be revised. Indeed, in agreement with the rules of homeostatic plasticity, the susceptibility of cortical neurons to change their excitability in response to a brain stimulation paradigm as well as the direction of the excitability shifts can be adjusted to the level of activity prior to conditioning. On this basis, it is conceivable that in migraine an abnormal high interictal excitability level could affect the response to various paradigms of brain stimulation, giving rise to inhibitory responses to high stimulation intensity. Further support for this hypothesis was given in a recent study by Cosentino et al. (2012), in which healthy volunteers showed an inhibitory response to HF-rTMS trains, similar to that of migraineurs, when the level of cortical excitability was previously increased by anodal tDCS.

Evidence regarding abnormalities of homeostatic plasticity has been reported previously in a combined tDCS and 5-Hz rTMS study where migraine motor cortex showed less inhibitory response following anodal preconditioning (Antal et al., 2008). Data supporting dysfunctional homeostatic plasticity has also come from two neuroimaging studies (Sandor et al., 2005; Siniatchkin et al., 2012) that investigated excitability and information processing between attacks in the visual cortex of patients with migraine, and found abnormal homeostatic responses to visual stimulation resembling those observed in the motor cortex. Siniatchkin et al. (2012) also revealed, by means of proton magnetic resonance spectroscopy, higher interictal glutamate/creatine ratios compared with those in healthy subjects, suggesting an altered glutamatergic neurotransmission.

**Migraine cycle and migraine chronification: the contribution of neurostimulation techniques**

Whatever the interplay between facilitatory and inhibitory circuits in migraine pathophysiology, a critical aspect concerns their role in the variations of cortical excitability in the ictal and interictal phases of migraine cycle and in the process underlying migraine worsening and chronification. In this respect, the relationship between intracortical circuits and the activity of the thalamocortical loops and brainstem monoaminergic nuclei could be of particular relevance.

**Migraine cycle.** Prominent electrophysiological changes have been observed between paroxysms (ictal period) and pain-free periods (interictal). It is well established that habituation/dishabituation, cortical excitability, thalamocortical activity, and serotonin metabolism fluctuate over time in relation to migraine attacks (Coppola et al., 2009). In the period immediately preceding an attack and during the attack itself, habituation of EPs is surprisingly normalized (Evers et al., 1999; Judit et al., 2000; Chen et al., 2009). Contextually, as revealed by neurophysiological and neuroradiological studies, thalamocortical activity as well as brain serotonin synthesis increases (Coppola et al., 2005, 2009; Sakai et al., 2008). This evidence has been considered to support the hypothesis of an interictal reduced basal cortical preactivation from subcortical structures that instead, during attacks, increase their level of activity, favoring cortical activation and restoring of habituation.

**Homeostatic plasticity and pathophysiological hypotheses**

According to the Bienenstock–Cooper–Munro model (Bienenstock et al., 1982), the existence of sliding modification thresholds for inducing long-term potentiation (LTP) and long-term depression (LTD) could also allow us to interpret apparently conflicting findings in patients with migraine. Indeed, if we interpret the paradoxical “facilitatory” response to LF-rTMS seen in migraine as due to a cortical hyperexcitability, the paradoxical “inhibitory” response to HF-rTMS could be better explained by inhibitory mechanisms of homeostatic plasticity. This point of view could provide an alternative interpretation of the effect of HF-rTMS in restoring habituation to VEPs. Indeed, dishabituation to EP experiments in migraineurs has been interpreted by some authors (Coppola et al., 2009) as the result of a low baseline excitability level in which repetitive stimuli do not cause decreased response amplitudes due to a floor effect. Following this, the recovery of habituation by means of HF-rTMS has been explained as consequence of increased cortical excitability. Alternatively, in light of the rules of homeostatic plasticity, we could consider migraine dishabituation as due to hyperexcitability, which could be reverted by HF-rTMS.

To summarize, evidence regarding dysfunction of presynaptic homeostatic plasticity with bimodal hypersensitive and hyporesponsive patterns, depending on stimulation intensity, strongly invokes mechanisms of homeostatic plasticity that seem in turn able to explain the apparently contradictory findings of neuromodulation studies in migraine.
This, however, appears to contrast with other evidence showing decreased excitability of visual cortex during migraine attacks (Siniatchkin et al., 2009) and motor cortical hyporesponsivity to HF-rTMS trains (Conte et al., 2010). According to this, we can also hypothesize an opposite condition in which excessive cortical activity at baseline could downregulate subcortical structures projecting to the cortex. This could represent a protective homeostatic mechanism likely mediated by bidirectional connections between cortex, thalamus, and brainstem nuclei. If so, during an attack subcortical structures could increase their activity as a consequence of the reduced cortical excitability – a compensatory phenomenon.

**Migraine chronification.** Changes in cortical excitability have also been invoked in the mechanism of migraine chronification, which has been suggested to some extent to represent a prolonged ictal state (Coppola and Schoenen, 2012). Chen and colleagues (2011), in a magnetoencephalographic study in patients with chronic migraine, first described changes in visual excitability (increased amplitude of the evoked response of the first block, normal habituation to repeated stimulation) similar to that observed in the ictal phase in episodic migraine (Chen et al., 2009). The authors interpreted these data as resulting from a condition of impaired central inhibition, in agreement with the evidence of greater impairment of inhibitory activity (assessed by TMS interference MSPA technique) in the visual cortex of chronic versus episodic migraineurs (Aurora et al., 2010). This could be partly in contrast with the hypothesis of prolonged ictal state, because the only study directly exploring the activity of inhibitory circuits (through MSPA) found a change toward increasing rather than reducing occipital inhibition, going from the interictal to the perictal phase of episodic migraine (Siniatchkin et al., 2009). Moreover, a difference has also been found with respect to the ictal state in a somatosensory EP study of patients with chronic migraine and drug overuse, where habituation was shown to be impaired (Coppola et al., 2010). The reason for such differences is not clear; it could be that cortical inhibitory circuits, which are activated during the attack in episodic migraine (perhaps as antinociceptive mechanisms), could progressively lose their efficiency as chronification develops, becoming even more impaired in the condition of drug overuse. Whatever the role played by inhibitory circuits, the changes observed suggest a tighter pathophysiological link between abnormal cortical excitability and mechanisms of dysfunctional nociceptive control operating in migraine chronification, further underlining the role of cortical and subcortical interaction in migraine. Together with the above-mentioned dysfunctions in cortical excitability, patients with chronic migraine showed: (1) significantly greater and persistent activation of brainstem structures involved in nociception with functional neuroimaging (Aurora et al., 2007; Aurora, 2009); and (2) more relevant neurophysiological and clinical signs of central sensitization, which is considered to represent the key mechanism involved in pain maintenance and chronification (Sandrini et al., 2002; Cooke et al., 2007).

**Neurostimulation and effects of preventive drugs in migraine**

In 2006, Ayata and colleagues showed that drugs that are effective in migraine prevention are also able to inhibit CSD experimentally in animals, thus providing a potential link between cortical excitability and efficacy. Several neurostimulation studies have been performed to explore this issue, evaluating the effects of drugs on different parameters of cortical excitability and the relationship with clinical measures in patients with migraine. These studies have given interesting results demonstrating the ability of drugs to modulate cortical excitability parameters, often providing an argument in favor of specific hypotheses. For instance, the ability of valproate, which is considered to act principally as a GABA agonist, to normalize parameters such as PT (Mulleners et al., 2002) and paradoxical responses to 1-Hz rTMS (Palermo et al., 2009), has given support to the role of suggested impairment of inhibitory circuits as a putative pathophysiological factor in migraine. Interestingly, inhibitory results have also been observed for other antiepileptic drugs. In the study by Artemenko et al. (2008), topiramate was found to reduce motor and visual cortex excitability, increasing PT and MT values; this drug was also able to change the responses to the MSPA test, perhaps by restoration of inhibitory circuits in the visual cortex of patients with migraine (Aurora et al., 2010). Levetiracetam demonstrated the ability to reduce motor cortical excitability increasing MT, reducing the abnormal MEP potentiation in the MEP recruitment curve, and abolishing the facilitatory effects of short-term plasticity observed with low-intensity 5-Hz rTMS trains (Brighina et al., 2011; Cosentino et al., 2011).

More interestingly, and in agreement with observation of Ayata et al. (2006), drugs not directly targeted to cortical excitability, such as beta-blockers, were also able to exert inhibitory modulation on visual cortical excitability parameters (PT reduction), while showing no effect on the motor cortex (Gerwig et al., 2012).

Unfortunately, in these studies no relevant evidence was provided about the role of excitability modulation induced by the drugs on clinical measures of efficacy, because correlation between these parameters was lacking. Thus, the majority of reports concluded...
by hypothesizing the existence of partially separate mechanisms for the effect on clinical outcome and on cortical excitability.

**NONINVASIVE NEUROSTIMULATION FOR THE TREATMENT OF MIGRAINE**

In recent years there has been particular interest in non-invasive brain stimulation techniques including TMS, rTMS, and tDCS as potential therapeutic approaches for migraine (Lipton and Pearlman, 2010). The mechanistic bases for such treatment strategy are: (1) the ability of TMS to interfere with ongoing electrical brain activity, so disrupting the abnormal neural changes underlying attack (CSD); and (2) the long-term plastic effects of rTMS or tDCS, which are able to normalize cortical excitability or modulate the neural circuits involved in pain control. Moreover, TMS, rTMS, and tDCS are safe and can be used without risk, even in repeated stimulation sessions (Dodick et al., 2010).

Transcranial magnetic stimulation for treatment of migraine attacks

CSD, in addition to being the basis of migraine aura owing to its ability to activate the trigeminovascular system, is considered potentially to be the first step for migraine pain. Moreover, some authors suggest that, in MwA, CSD occurring in silent cortical regions could also initiate the attack (Bolay et al., 2002; Ayata, 2010). Even if this potential role for CSD remains more critical, a tighter link between CSD, cortical excitability, and migraine mechanisms has been demonstrated recently in experimental animals, where drugs effective in migraine prevention were able to inhibit CSD (Ayata et al., 2006). On this basis, the ability to abort CSD would represent a critical target for treatment.

Recently, TMS has been shown to inhibit CSD experimentally in animals, thus demonstrating the potential to stop an aura and the subsequent headache in migraine (Brighina et al., 2004). On the basis of the hypothesized role of dysnociception as a pathogenetic factor in migraine chronification, the rationale was to potentiate the activity of an area that is known to exert an important role in pain control. We studied 11 patients who underwent 12 stimulation sessions (on alternate days), each consisting of 10 trains of 40 TMS pulses, separated by a 30-second pause, delivered at 20 Hz frequency and 90% MT intensity. Patients were assigned randomly to receive active (6 patients) or sham (5 patients) treatment. Treatment was effective, significantly reducing outcome measures (migraine attacks, drug consumption, headache index) in the month during and following stimulation with respect to baseline, whereas no effect was observed in sham-treated patients (Fig. 47.5). rTMS was well tolerated and no relevant side-effects were reported.
Teepker et al. (2010) used low-frequency (1 Hz) rTMS as preventive treatment for migraine. The rationale was to use inhibitory rTMS frequency to normalize cortical excitability, which is considered to be increased in migraine. These authors treated 27 migraineurs with 2 trains of 500 magnetic pulses at 1 Hz, delivered over the vertex daily for 5 consecutive days. A trend toward amelioration was observed after versus before rTMS in the real rTMS but not in the sham rTMS group; however, no statistically significant difference was observed between (real versus sham) and within (before versus after rTMS) groups. Another recent study used a similar rationale with the aim of reducing excitability of the visual cortex by means of cathodal tDCS (a polarity known to induce cortical inhibition) in patients with MwA (Antal et al., 2011). The authors treated 13 patients with real and 13 with sham cathodal tDCS, delivered over V1 cortex in sessions of 15 min in at 1 mA intensity 3 times per week for 6 weeks (18 stimulation sessions). Cathodal tDCS was partly effective, significantly reducing the duration of attacks, the intensity of pain, and the number of migraine-related days, but not the frequency of the attacks compared with the baseline period. Moreover, compared with the sham group, only the intensity of the pain was significantly reduced poststimulation.

Considering the few trials performed and the small series of patients studied, no conclusion can be drawn from these studies. However, it seems that strategies aiming to favor pain control potentiating antinociceptive brain areas are probably more effective with respect to the target of reducing cortical excitability. This could be due to greater relevance of dysnociceptive mechanisms or to possible paradoxical facilitatory effects of inhibitory LF-rTMS and cathodal tDCS secondary to homeostatic plasticity mechanisms. With regard to dysnociception, cortical neuromodulation (prefrontal and motor cortex) has been shown to be effective in many pain states (Zaghi et al., 2011), and in a recent study motor cortex HF-rTMS reduced LEP amplitude more in migraineurs than in controls (de Tommaso et al., 2010). Regarding cortical excitability, normalization of neurophysiological parameters in migraine was induced by HF-rTMS but not LF-rTMS, and persistent effects on recovery of habituation were found when repeated.
HF-rTMS stimulation sessions were used (Fumal et al., 2006). Further studies are needed to determine the optimal stimulation parameters (intensity, frequency, number and duration of stimulation sessions). Concerning this last point, it would be particularly useful to develop self-activable stimulation devices (for both tDCS and rTMS) that patients could use at home for symptomatic and preventive treatment. In this respect, tDCS, which requires only simple battery-driven equipment, could have the advantage of being a less expensive and easier to use portable device for patient self-use.

CONCLUSION

Noninvasive brain stimulation techniques are finding growing application in the migraine field, providing an important contribution to our understanding of migraine pathophysiology, and offering new opportunities for both symptomatic and preventive treatment. These techniques have the great advantage of being noninvasive and painless, and therefore applicable in awake subjects in different experimental paradigms. Moreover, as evidenced by many reports, they are safe and could be used without risk for repeated application in therapeutic settings. As concerns pathophysiological hypotheses, even if definite conclusions cannot yet be drawn from the evidence reported, modulation studies with rTMS and tDCS have been particularly interesting in revealing abnormalities not only in excitability but also in mechanisms of cortical plasticity and responsivity.

These changes, irrespective of the different – and even opposing – interpretative hypotheses, ranging from hyperexcitability, reduced inhibition, or reduced activation of sensory cortices, could find explanation in a more comprehensive view based on the principles of homeostatic plasticity. Recent evidence also suggests dysfunction in short-term glutamate-dependent plasticity, with both hyperexcitability at low, near-threshold activation and self-limiting, inhibitory responses at high stimulation intensity. Interestingly, dysfunctions of presynaptic plasticity could result from abnormalities of membrane channels (in agreement with experimental migraine models), and the inhibitory response pattern at high-magnitude stimulation is converging with evidence regarding the ability of HF-rTMS to normalize neurophysiological parameters in migraine, establishing new potential targets for future therapeutic application.

Neuromodulation approaches for headache treatment provide consistent evidence regarding the efficacy of TMS for attack treatment, at least in patients with MwA. Far less evidence is available about the efficacy of neurostimulation for preventive treatment.

Further controlled studies in large patient cohorts, exploring the approach to increase nociceptive control and to modulate cortical excitability according to the principles of homeostatic plasticity, could help to assess the real efficacy of each neurostimulation technique. Moreover, the generation of easy and low-cost stimulation devices for patient self-use would likely extend the applicability of these techniques, making them new, available, and effective options for symptomatic and prophylactic treatment of migraine.

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