



# Highlights in migraine electrophysiology: are controversies just reflecting disease heterogeneity?

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## Purpose of review

In migraine, the brain is 'hyperresponsive', which refers to a deficit of habituation to repeated sensory stimuli between attacks. This deficit normalizes in peri-ictal and ictal phases. A decreased cortical preactivation of thalamo-cortical origin and an impaired intracortical inhibition are probably involved in its pathophysiology.

## Recent findings

The reality of a habituation deficit of visual evoked potentials, a neurophysiological 'hallmark' of interictal migraine, has been questioned. Blinding may be an issue, but some genetic, environmental, or behavioural differences could also exist between populations. A habituation deficit is found interictally in other sensory modalities, and strongly depends on the time of the recordings within the migraine cycle. An impaired thalamocortical drive is demonstrated in interictal phase, and normalizes in ictal phase as well as in chronic migraine, where a strength enhancement of primary cortical activation is observed. An interictal dysexcitability, of subcortical or primary cortical origin, is suggested by magnetic stimulation. These phenomena could occur in varying degrees depending on patients and on the migraine cycle, and account for the heterogeneity of electrophysiological results.

## Summary

Finding a reliable electrophysiological biomarker for such a multifaceted and cycling disease as migraine is still a challenge. A better standardization of protocols would be worthwhile.

## Keywords

electrophysiology, evoked potentials, habituation, magnetic stimulation, migraine, pathophysiology

## INTRODUCTION

Migraine is a widespread neurological disorder, and ranks 25th according to the Global Burden of Disease Study [1]. In its common form, migraine is characterized by recurrent attacks of moderate-to-severe throbbing headache pain, increased by physical activity, and accompanied by nausea/vomiting and/or hypersensitivity to sensory inputs [2]. Migraine with aura is associated with transient neurological symptoms preceding or accompanying the headache [2].

Electrophysiology is particularly suitable to study the nervous system of human beings. It is noninvasive, riskless, and relatively easy to perform in terms of material cost and transportation. Briefly, the different components of the nervous system generate an electrical signal that reflects the summation of several action potentials. The response of the nervous system to various types of stimuli can also be recorded through methods like stimulus-related evoked potentials (with visual, sensory,

auditory stimuli, etc.) or transcranial magnetic stimulation (TMS) which allows to evaluate the temporal changes in cortical excitability, and is able to induce longer-lasting neuroplastic changes. Electrophysiology and related methods have the advantage to be more accurate in time and accessible than neuroimaging modalities, being thus useful complementary techniques to assess the pathophysiology of primary headaches.

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## KEY POINTS

- Electrophysiology provides a noninvasive and easy approach of the ongoing nervous system activity, and is thus particularly useful to study functional brain disorders like migraine.
- Lack of cortical habituation to repeated sensory stimuli is found more frequently in migraine patients between attacks but varies according to the time of the recordings in the migraine cycle.
- Between attacks, migraine is associated with an impaired thalamo-cortical drive that could be proportional to disease severity, and with a cortical dysfunction probably because of an impaired inhibition. Whether the latter is the consequence of the former remains debated. Ictally and in chronic migraine, a sensitization occurs with signs of cortical activation.
- Genetics and migraine subtypes could explain some heterogeneity within the results.
- Methodological accuracy (especially regarding the migraine cycle) and objectivity appear of highest importance when considering electrophysiological recordings in migraine.

## WHAT WE KNEW: FACTS AND CONTROVERSIES

Abnormalities of cortical information processing occurring in migraine patients have been described since the late forties [3,4].

Habituation is a behavioural response decrement that results from repeated stimulations and does not involve sensory adaptation or fatigue, that is, a decrease in peripheral receptor activity [5]. It is considered as a fundamental adaptive behaviour of the nervous system that allows selection of salient information among all ambient stimuli, and is involved in learning and memory. In episodic migraine patients recorded between attacks, earlier electrophysiological studies demonstrated on average an habituation deficit to repetitive stimuli, regardless of the modality of stimulation, that is, the neuronal population that gets stimulated, with the only exception of olfactory [3,4]. This habituation deficit was considered as the most redundant electrophysiological abnormality of migraine populations in interictal state, the more that it had also been found with cognitive event-related potentials, at subcortical level, and with innocuous and noxious modalities [3,4]. However, not all studies were able to reproduce this neurophysiological 'hallmark'. It was hypothesized that methodological differences could account for discrepancies: the lack of habituation was found in studies using peculiar

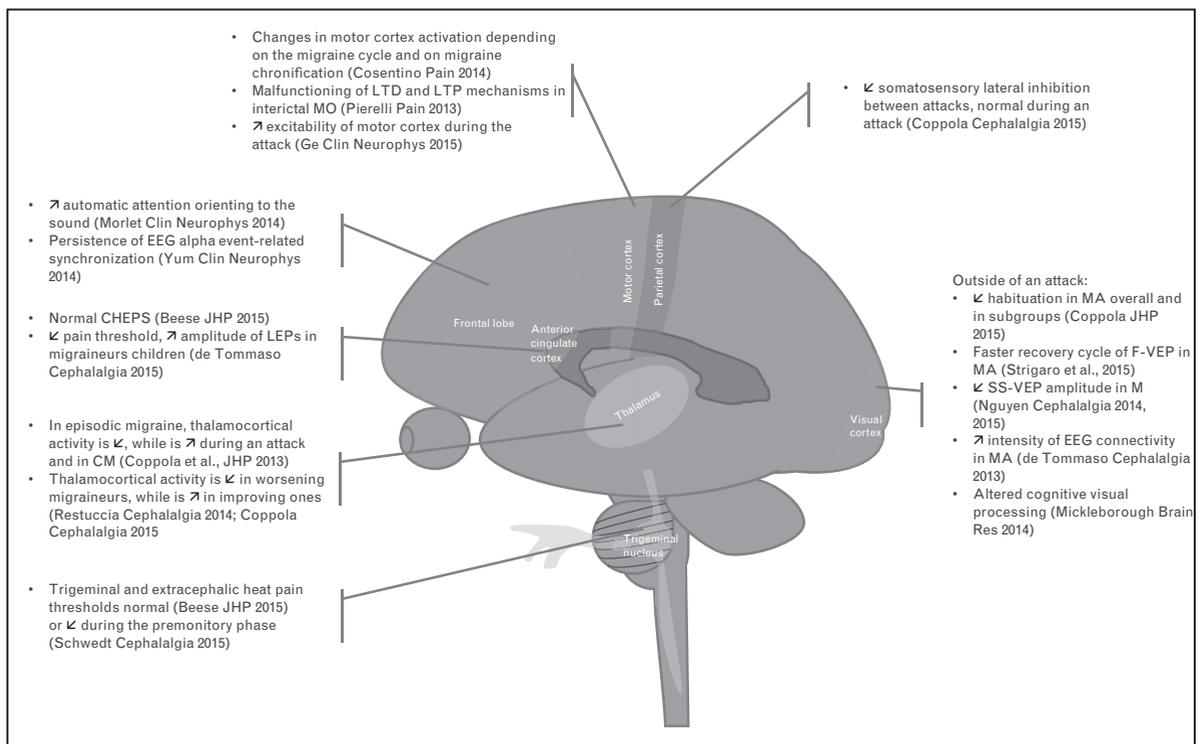
parameters [4]. It was also demonstrated that heterogeneity of habituation levels could be determined by inherited factors [6–9], by different patient's clinical features [10,11<sup>¶</sup>] and by environmental factors like some acute [12] and preventive drugs [13]. Surprisingly, habituation normalizes during the migraine attack, whereas clinically this migraine phase is usually associated with a more pronounced hypersensitivity to external stimuli and is normal in the peri-ictal period, as well as in chronic migraine thus considered as a 'never ending attack' [14]. Being a group and not an individual trait, the lack of habituation cannot be considered as a diagnostic biomarker of migraine 'per se.'

The other controversy in migraine electrophysiology was the baseline cortical excitability level assessed by TMS (phosphene or motor threshold) and evoked potentials initial amplitude: some studies suggested that the cortex was hypoexcitable between attacks (increased thresholds) [15], whereas others argued that it was hyperexcitable (decreased thresholds) [16]. Methodological issues have also been highlighted to explain the discrepancies [4]. Low initial evoked potential amplitude, that is, reduced cortical preactivation, seemed correlated to deficient habituation in visual, somatosensory, and auditory evoked potentials, suggesting that the latter could be the consequence of the former [4,17] (Fig. 1).

Two hypotheses that attempt to explain the lack of habituation found interictally in episodic migraine have since been debated. An imbalance between inhibitory and excitatory cortical mechanisms (reduced intracortical inhibition or increased excitation) was suggested by studying peripheral responses to TMS [16,18]. Coppola *et al.* [19] proposed a 'unifying' hypothesis, based on studies of high-frequency oscillations (HFOs): a thalamocortical dysrhythmia would explain the increased cortical excitability and deficient inhibition, and this impaired thalamocortical drive could lower the level of cortical preactivation, resulting in a dysfunction of both inhibitory and excitatory cortical neurons. Decreased inhibition and cortical preactivation may coexist, as the latter can promote the former through a reduction of lateral inhibition. The final common pathway is a cortical 'hyperresponsiveness'.

## VISUAL PROCESSING SEEMS PREDOMINANTLY IMPAIRED IN MIGRAINE

Migraine is commonly associated with photophobia in ictal period. In some patients an increased light sensitivity may persist in peri or interictal phases (Table 1). Many recent electrophysiological studies



**FIGURE 1.** New electrophysiological studies in migraine.

have investigated the visual system, particularly through visual evoked potentials (VEP). Briefly, VEP record the mass activity of visual cortical neurons in response to visual stimuli – flashes or pattern reversal checkerboards (PR-VEP) – which can be delivered at various frequencies: low, that is, less than 3.5 Hz, high rates or steady-state (SS-VEP) more than 3.5 Hz. PR-VEP studies performed previously in migraine showed an overall habituation deficit of VEP amplitudes in the interictal phase [usually of the first component of the visual evoked potentials (N1P1) reflecting the striate cortex activation] that normalized during the attack and in the peri-ictal phase (time interval of  $\pm 48$ –72 h before and after the attack) [4]. Between attacks the initial VEP amplitude tended to be lower in migraineurs compared with healthy study participants, suggesting a reduced visual cortex preactivation. However, some studies were not able to reproduce these results. Methodological differences were previously believed to be responsible for these discrepancies: usually stimulations with smaller checks and higher contrast lead to a more pronounced habituation [35]. The habituation deficit of evoked potentials was generally considered as a neurophysiological ‘hallmark’ of migraine between attacks [3], and used as rationale for many studies, but its existence has been recently questioned by a group of authors [30<sup>■</sup>,36]. To address this issue, they used parameters that had been

shown to induce a lack of habituation in former trials, included a large population and repeated the assessments (4 VEP/study participant). VEP recordings and analyses were blinded. As they failed to retrieve any lack of VEP habituation or decreased initial VEP amplitude in patients, the authors stressed that the argument of different stimulation parameters was no longer convincing, the more that one previous study was also negative [36]. They concluded that a lack of blinding might have biased positive results (expectation of the examiners), and that VEP habituation deficit was not a reliable biomarker of migraine [30<sup>■</sup>]. Apart from this study however, other investigations from at least three independent groups have observed an interictal VEP habituation deficit in their respective populations using a blinded off-line design analysis [11<sup>■</sup>,20<sup>■</sup>,21,32<sup>■</sup>], even if the reproducibility of some recordings was rather disappointing [32<sup>■</sup>]. Lack of blinding is obviously not the sole explanation for the discrepancies; since both positive and negative studies were actually not completely blinded [11<sup>■</sup>], and researchers who found no VEP abnormalities in migraineurs had negative results irrespectively of being blinded or not [37]. The time of recording seems to be fundamental in determining the final neurophysiological outcome since VEP habituation with stimulus repetition decreases with the distance from the last migraine attack, that is, the level of habituation strongly depends on the point where

**Table 1.** Recent electrophysiological trials comprising the visual system with their respective characteristics and outcomes

References	Populations migraine phase	Test	Results
Ambrosini <i>et al.</i> [20 <sup>***</sup> ]	MO = 13 interictal Healthy Volunteers = 15	PR-VEPs and magnetophosphene threshold	Lack of habituation in migraineurs but MPT is normal No correlation between MPT and habituation in neither group
Bednár <i>et al.</i> [21]	MIG = 39 mixed population (19 interictal and without prophylaxis) Healthy Volunteers = 36	Pattern reversal (high and low-contrast) and motion-onset VEPs	Blinded assessment lack of habituation in migraineurs other VEPs modalities do not increase the test sensitivity
Buonfiglio <i>et al.</i> [22]	Healthy Volunteers = 30	VEPs and analytic cognitive style (psychological evaluation)	Deficient VEP habituation is found in analytic study participants
Coppola <i>et al.</i> [11 <sup>†</sup> ]	MA = 27; MA+ = 20; Healthy Volunteers = 30	VEP	Habituation is deficient in MA and MA+ VEP amplitudes greater in MA+ compared with Healthy Volunteers: preactivation cortical excitability could be higher
de Tommaso <i>et al.</i> [23 <sup>†</sup> ]	MO = 19; MA = 19; Healthy Volunteers = 11	Ongoing EEG under photic stimulation	Phase synchronization increased in alpha band in MO, and decreased in $\beta$ band in MA. Divergence of ongoing EEG activity between MO and MA might reflect different connectivity patterns
Fogang <i>et al.</i> [24]	MO = 171; MA = 61; Chronic Migraine = 48; MOH = 37; Healthy Volunteers = 24	EEG photic driving assessed by visual inspection vs. computer spectral analysis	Visually-assessed 20 Hz photic driving is of little diagnostic utility and overestimated in migraine; Spectral analysis showed increased photic driving in subgroups of migraineurs and could be of pathophysiological interest
Gantenbein <i>et al.</i> [25 <sup>†</sup> ]	MO = 11 Interictal Healthy Volunteers = 11	EEG H-response with increasing flash stimulation of 10–40 Hz	Higher photic driving in migraineurs above 26 Hz, H-response different between groups High inter-test reliability
Jancic <i>et al.</i> [26]	MA = 38; MO = 38; Teenagers; Healthy Volunteers = 38	PR-VEPs	Right-left eye N2 differences in MA compared with MO and Healthy Volunteers; in MA, negative correlation between amplitude and age of onset/age of patients; tunnel vision during aura associated with lower VEPs amplitudes (N1P1 and P1N2)
Nguyen <i>et al.</i> [27]	MA = 15; MO = 15; interictal; Healthy Volunteers = 21	SS-VEPs 0–97% contrast	Supersaturation – relative reduction in SS-VEP response with increasing contrast in migraineurs; supports excitatory-inhibitory imbalance
Nguyen <i>et al.</i> [28 <sup>†</sup> ]	MO = 11; MA = 6; Postictal; Healthy Volunteers = 26	Perimetry/visual field; PR ERGs; SS-VEPs; Performed at different durations postmigraine	Visual field defects are most common closer to the attack; ERG is normal but SS-VEPs amplitudes are reduced in migraineurs; Results suggest retinal and cortical dysfunctions
Omland <i>et al.</i> [29]	MIG = 25 interictal (14 MO and 11 MA); MIG = 7 preictal; Healthy Volunteers = 32	VEPs before and after 10 Hz rTMS	rTMS reduced habituation only in migraineurs, and may suggest an increased responsiveness linked to an interictal cortical dysfunction
Omland <i>et al.</i> [30 <sup>†</sup> ]	MIG = 41; interictal; Healthy Volunteers = 30	PR-VEPs blinded assessment	VEP habituation does not differ between groups using 16 checks and blinded analysis.

Table 1 (Continued)

References	Populations migraine phase	Test	Results
Rauschel <i>et al.</i> [31]	MO = 22; interictal; Healthy Volunteers = 24	Magnetic suppression of perceptual accuracy	No evidence of MSPA, that is, of reduced occipital cortex inhibition, in migraine without aura (unlike in migraine with aura and chronic migraine); good test-retest reliability but few study participants had a second evaluation
Rauschel <i>et al.</i> [32 <sup>■</sup> ]	MIG = 41; interictal; Healthy Volunteers = 40	Test-retest reliability of VEPs	Lack of habituation of VEPs in migraineurs. Low test-retest reliability of VEP habituation.
Rocha <i>et al.</i> [33]	MA = 11; MO = 12; phase ?; Healthy Volunteers = 11	MPT before and after inhibitory tDCS therapy	Lower MPT in migraineurs; no difference between MO and MA; → cortical hyperexcitability in migraineurs? No change of excitability after tDCS though patients improved
Strigaro <i>et al.</i> [34]	MO = 13; MA = 13; Healthy Volunteers = 22	Paired-pulse flash-visual evoked potential	Defective neural inhibition in MA

EEG, electroencephalography; ER, event-related; HFOs, high-frequency oscillations; MA, migraine with aura patients; MA+, migraine with complex aura (visual+sensory/motor symptoms); MIG, migraine patients (all types); MO, migraine without aura patients; MOH, medication-overuse headache patients; MPT, magnetophosphene threshold; PR-ERGs, pattern-reversal electroretinograms; PR-VEPs, pattern reversal VEPs; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VEP, visual evoked potentials.

the patient is in the migraine cycle [38]. Lack of habituation may be found more prominently in analytic study participants [22]. Finally, a genetic component could likely influence the results. VEP habituation is similar between pairs of parents and their children [39]. Moreover, although no lack of habituation was found in populations from northern Europe [30<sup>■</sup>,36], this trait was demonstrated by several groups of middle or southern Europe [11<sup>■</sup>,20<sup>■</sup>,21,32<sup>■</sup>], where the genetic heritage is probably different.

Other interesting results on migraine pathophysiology were recently published using various techniques allowing visual system assessment (Table 1). Coppola *et al.* [11<sup>■</sup>] found that the initial amplitude of VEP responses was higher in patients suffering from migraine with complex aura (MA+, i.e. with sensory disturbances and/or dysphasia) compared with healthy volunteers), but was similar between patients with pure visual aura (MA) and healthy volunteer. Various aura phenotypes might thus be underpinned by different pathophysiological mechanisms, with a greater initial cortical excitability in MA+. Further evidence for altered cortical excitability in MA came from a study using paired-pulse suppression of flash-VEP (F-VEP). Strigaro *et al.* [34] found reduced paired-pulse inhibition of F-VEP amplitude in MA patients compared with migraine without aura (MO) and healthy volunteers, which was interpreted as evidence for defective inhibitory mechanisms in the visual cortex of MA patients.

The level of cortical excitability can also be evaluated using the threshold of phosphenes induction with magnetic stimulation over the visual cortex [magnetophosphenes threshold (MPT)]. A novel study [20<sup>■</sup>] showed that despite a significant habituation deficit associated with a trend to lower cortical preactivation (VEP initial amplitude), MPT was normal in MO interictally. No correlations were found between the lack of habituation or VEP initial amplitude, and the MPT, whatever the group. Although MPT represents a punctual measure of cortical excitability and has shown a high variability between migraineurs, habituation would involve a distinct and dynamic phenomenon, reflecting a hyperresponsiveness of the visual cortex in patients with MO, without any hyperexcitability per se. These abnormalities might be caused by different mechanisms that might be either of neuroanatomical (striate vs. extrastriate cortices activation, involvement of other cortical circuits within the same brain area), and/or of functional origin. In contrast, a study performed by the Norwegian team [29] found no baseline difference between migraine and controls in terms of initial PR-VEP amplitudes, whereas after an excitatory (10 Hz) repetitive TMS (rTMS) of the visual cortex, migraine patients developed a lack of PR-VEP habituation, which differed according to the migraine phase and check size. The authors explained their findings by a distinct impairment of magnocellular and parvocellular pathways depending on the phase of the migraine cycle.

Using steady-state [SS-VEP, which induces an alignment of background electroencephalography (EEG) activity], a VEP amplitude reduction was described in migraine between attacks [28<sup>■</sup>,27], and particularly enhanced by contrast increase. This interictal altered contrast gain could result in a visual aversion to high-contrasted stimuli in migraineurs and would reflect an imbalance of excitatory and inhibitory processes [27]. Subtle coexistent retinal and cortical dysfunctions were suggested in migraine by monocular or binocular visual field defects (perimetry), more marked in close relation to the attack, but not correlated with the SS-VEP changes [28<sup>■</sup>]. In another study, researchers studied visual cortex excitability by the application of a single magnetic pulse over the occipital cortex which physiologically impaired recognition of letters presented on a screen just before the pulse, namely magnetic suppression of perceptual accuracy (MSPA, [31]). MSPA was previously found reduced in MA and chronic migraine and interpreted as a result of deficient intracortical inhibition (the magnetic pulse was supposed to activate the inhibitory interneurons). Recently, no interictal reduction of MSPA was found in MO with frequent attacks, suggesting intracortical inhibitory mechanisms are not impaired in MO [31]. This is in contradiction with the hypothesis of a MSPA reduction in proportion to migraine severity, reaching its maximum in chronic migraine patients [40]. Migraine also appears to affect postsensory perception systems and especially cognitive visual processing [41]. Finally, a new interest seems to resurge for EEG recordings in migraine research. Photic driving, that is, the tendency of EEG rhythms to synchronize with external visual repetitive stimuli, was observed previously in migraine patients using medium stimulation frequencies ( $\pm 20$  Hz, H-response) [42]. Visually assessed photic driving seems of little diagnostic utility in migraine (specificity 69.36%), but significant differences have recently been found between migraine subtypes when using computer spectral analyses [23<sup>■</sup>,24]. de Tommaso *et al.* [23<sup>■</sup>] showed that EEG activity during visual stimulation differed between MA and MO (phase synchronization of  $\alpha$  and  $\beta$  rhythms), reflecting dissimilar connectivity patterns. In general, photic driving occurs more frequently in migraineurs, with a higher discriminating power when photic stimulation frequency ranges from 20 to 25 Hz [25<sup>■</sup>]. A high interest reliability was described in 22 study participants, when recordings were done the same day [25<sup>■</sup>]. This promising approach could lead to disentangle more reliable electrophysiological biomarkers in the future.

### **SOMATOSENSORY AND PAIN-RELATED SYSTEMS (QUANTITATIVE SENSORY TESTING, CONTACT HEAT-EVOKED POTENTIALS, SOMATOSENSORY EVOKED POTENTIALS, LASER EVOKED POTENTIAL)**

See Table 2. Former studies of electrical and pressure pain thresholds were usually normal in migraineurs when measured interictally. Two recent studies performed thermal quantitative sensory testing, but their results were conflicting [43<sup>■</sup>,51<sup>■</sup>]. Beese *et al.* [43<sup>■</sup>] found that quantitative sensory testing was similar between controls and episodic migraineurs, whereas Schwedt *et al.* [51<sup>■</sup>] retrieved a lower heat pain threshold in migraineurs (head/arm). The latter involved larger groups (112 vs. 20 migraineurs), but the migraine population was quite intermixed. However, their initial results persisted even when they excluded chronic migraine and patients who were in pain during the testing. The patients involved in both studies were different: young episodic migraineurs recruited outside the consultation [43<sup>■</sup>] vs. more severely affected patients coming from headache clinics, with higher anxiety and allodynia scores [51<sup>■</sup>]. A subanalysis on 31 patients [51<sup>■</sup>] demonstrated a positive correlation between the number of hours until next headache attack and trigeminal and extracephalic heat pain thresholds that could perhaps reflect an early manifestation of the migraine attack per se (the so-called premonitory phase), through excitatory/inhibitory imbalance of pain-controlling brain areas. Contact heat evoked potentials were similar between controls and interictal migraineurs, and a lack of habituation appeared in patients but also partly in controls when a distraction task was performed during the stimulation [43<sup>■</sup>]. Why authors used a thermal stimulation delivered within the second trigeminal branch innervations' territory (cheek) and not the first (forehead) is obscure. Laser is another means to deliver a thermal stimulus and has the advantage of avoiding a direct skin contact compared to contact heat-evoked potentials (CHEPs). Laser evoked potentials show signs of sensitization in young pain-free migraineurs, but no significant lack of habituation [46]. However, the latter authors did not control for proximity to the next attack.

Somatosensory evoked potentials (SSEPs) seem to be more reproductively disturbed in migraineurs, especially when HFOs are analysed. Two HFOs bursts can be extracted from broad band SSEPs: the early component thought to be generated by thalamo-cortical afferents (presynaptic), and the late component coming from cortical activation (postsynaptic). Previous works found out that reduced thalamic/thalamo-cortical activity occurred in episodic migraineurs between attacks, along with a

**Table 2.** Recent electrophysiological trials comprising somatosensory, motor and pain-related systems evaluation with their respective characteristics and outcomes

References	Populations migraine phase	Test	Results
Beese <i>et al.</i> [43 <sup>■</sup> ]	MA = 12; MO = 10; interictal; Healthy Volunteers = 22	Contact heat-evoked potentials and QST	QST similar between groups; no lack of habituation in MA/MO at baseline; Partial lack of habituation when a calculation task is performed
Coppola <i>et al.</i> [17]	MO = 34; interictal = 15; ictal = 19; chronic migraine = 19; Healthy Volunteers = 20	SSEPs and HFOs	Interictally: lack of habituation and reduced early HFOs and first block SSEPs amplitude. Ictally and in chronic migraine patients: habituation becomes normal and initial SSEP and late HFOs amplitudes are increased, suggesting sensory sensitization because of an increase of thalamo-cortical connections
Coppola <i>et al.</i> [44 <sup>■</sup> ]	MO = 24 interictal; MO = 17 ictal; Healthy Volunteers = 17	SSEPs, lateral inhibition of the N20-P25 component and HFOs	Lateral inhibition and thalamocortical activity were reduced interictally; lateral inhibition negatively correlated with migraine severity and positively correlated with thalamo-cortical activity
Cosentino <i>et al.</i> [45 <sup>■</sup> ]	MO = 66; MA = 48; chronic migraine = 14; inter, pre, post, and ictal phases; Healthy Volunteers = 20	Motor EPs after suprathreshold rTMS of M1 in various states of the migraine cycle	Facilitation or inhibition of MEP responses according to migraine state and attack frequency; changes in cortical excitability and fluctuations in the threshold for inhibitory metaplasticity may underlie attack recurrence
de Tommaso <i>et al.</i> [46]	Children MO = 35; interictal; Healthy Volunteers = 17	Laser evoked potentials	Symptoms of sensitization in migraineurs; lower pain threshold, higher N2P2 amplitude, and trend to deficient habituation
Ge <i>et al.</i> [47]	MO = 23; MA = 6; ictal; Healthy Volunteers = 29	MEG and finger-tapping task	Latency of motor-evoked magnetic fields evoked by finger movement is prolonged in migraineurs; higher odds of activation in the ipsilateral primary motor cortex and supplementary motor area in migraineurs
Kalita <i>et al.</i> [48]	MIG = 100 (EM, chronic migraine, MOH)	SSEPs	Lack of habituation in migraineurs; sensitization (amplitude) higher in migraineurs with allodynia
Pierelli <i>et al.</i> [49 <sup>■</sup> ]	16 MO; MO = 16; Healthy Volunteers = 15	Motor-evoked potential amplitudes before and after PAS	PAS10: increased amplitudes in MO; PAS25: potentiated MEP amplitudes in Healthy Volunteers
Restuccia <i>et al.</i> [50]	MIG = 25 (20 MO, 5 MA); Healthy Volunteers = 18	SSEPs and HFOs; Analysis of clinical fluctuations	Deficient habituation of N20 response; initial HFO component is smaller in worsening migraineurs
Schwedt <i>et al.</i> [51 <sup>■</sup> ]	MIG = 112; interictal/ictal; Healthy Volunteers = 75	Cutaneous heat pain thresholds	Lower heat pain thresholds in migraineurs. Positive correlation between pain threshold and time to next attack (Time to next attack known for 48 patients)

ER, event-related; HFOs, high-frequency oscillations; MA, migraine with aura patients; MA+, migraine with complex aura (visual+sensory/motor symptoms); MIG, migraine patients (all types); MO, migraine without aura patients; PAS, paired associative stimulation; QST, quantitative sensory testing; rTMS, repetitive transcranial magnetic stimulation; SSEPs, somato-sensory evoked potentials; tDCS, transcranial direct current stimulation.

lack of habituation of SSEPs, whereas central sensitization of the somatosensory cortex was suggested by increased initial amplitude of SSEPs in chronic migraineurs with medication-overuse headache (MOH) [12]. A recent trial recorded SSEPs and HFOs in episodic and chronic migraine without medication overuse [17]. Interictally, there was a lack of habituation of the cortical N20-P25 component of SSEPs, whereas in the ictal period and in chronic migraine

patients the habituation was normal, except for an initial N20-P25 amplitude increase, suggestive of sensitization. In the same line, early HFOs, reflecting thalamo-cortical activity, were reduced interictally and late HFOs were increased ictally and in chronic migraine patients, suggesting an enhancement of primary cortical activation strength, as a neurophysiological correlate of the central sensitization. Thus, chronic and ictal patients exhibit the same SSEPs and

HFOs pattern, but the late response differs from MOH where a further amplitude increase during additional stimulations is observed after an initial sensitization [12]. The same authors studied the degree of lateral inhibition within the somatosensory cortex, and showed that the percentage of somatosensory lateral inhibition was reduced in MO between attacks compared with healthy study participants, but was within the normal range ictally [44<sup>■</sup>]. The degree of lateral inhibition correlated positively with somatosensory thalamocortical activity and was inversely proportional to days elapsed since the last attack, severity of the migraine headache and attack duration. In consequence, reduced lateral inhibition could reflect migraine severity. That a worse clinical manifestation of migraine may be associated with low thalamocortical loop activity is also supported by the observations of Restuccia *et al.* [50] who found that early HFOs were smaller in patients who experienced an increase in the number of migraine attacks during the 6 months following the recording session (worsening migraineurs).

### STUDIES INVOLVING OTHER MODALITIES: MOTOR, AUDITORY, COGNITIVE

See Table 3. Motor evoked potentials (MEPs) are obtained using a TMS over the primary motor cortex

(M1) and correspond to an electrical signal recorded over the 'muscle' whose primary motor neurons get stimulated. Roughly, MEP amplitude depends on the excitability of the motor cortex. Some previous MEP studies performed in migraine have shown an abnormal and paradoxical excitability pattern, especially in migraine with aura and in the interictal period, but the available results again display some discrepancies, perhaps of technical origin. Various TMS stimulation protocols can be used to modulate MEP and noninvasively assess different aspects of cortical synaptic plasticity in humans. Cosentino and colleagues [45<sup>■</sup>] recently studied trains of 5 Hz rTMS delivered at suprathreshold MEP throughout various states of the migraine cycle: inter, pre, post, and ictal, and demonstrated fluctuations of MEP response according to the migraine state (facilitation or inhibition), and to migraine frequency. Trains of 5 Hz rTMS induced an inhibitory MEP response pattern that was similar in patients with high-frequency episodic migraine, patients in ictal state and a chronic migraine population. According to the authors, this pattern could mirror a reduced threshold for cortical inhibitory homeostatic responses, which would have a protective role in presence of a basically hyperactivated cortex, but would then become ineffective in preventing attacks because of an excessive lowering of the migraine threshold [45<sup>■</sup>]. The hypothesis of a

**Table 3.** Recent electrophysiological trials comprising cognitive tasks and auditory stimulation with their respective characteristics and outcomes

References	Populations migraine phase	Test	Results
Kropp <i>et al.</i> [52]	MO = 32; Healthy Volunteers = 16	CNV	Deficient or lack of habituation in migraineurs; higher CNV amplitudes in patients with longer disease duration (>120 months)
Mickleborough <i>et al.</i> [41]	MIG = 29; interictal; Healthy Volunteers = 29	ERPs to implicit evaluative analysis of visual images	Abnormal implicit evaluative processing of visual stimuli in migraineurs with lack of normal hedonic evaluation
Morlet <i>et al.</i> [53]	Menstrual MO = 22; various states of the cycle; Healthy Volunteers = 20	Auditory ERPs, mismatch negativity	Normal auditory sensory processing in migraineurs; attention orienting to sound income and sound deviance increased in migraineurs (frontal networks?)
Overath <i>et al.</i> [54]	MIG = 33	CNV; attention and information processing tests before and after aerobic exercise	Reduction of CNV amplitude and Trail Making Test A and B processing times after exercise; reduction of the migraine attack frequency; exercise could influence central information processing
Yum <i>et al.</i> [55]	MIG = 16; Healthy Volunteers = 16	EEG during auditory stimulation (ER synchronization and phase delocking of $\alpha$ waves)	$\alpha$ ER synchronization fading and phase delocking are deficient in migraineurs

CNV, contingent negative variation; EEG, electroencephalography; ER, event-related; MA, migraine with aura patients; MA+, migraine with complex aura (visual + sensory/motor symptoms); MIG, migraine patients (all types); MO, migraine without aura patients.

primary cortical dysfunction in migraine is not supported by another rTMS study [49<sup>■</sup>]. Paired associative stimulation (PAS) generates long-term depression or potentiation of cortical excitability through modulation of excitatory intracortical glutamatergic synapses [49<sup>■</sup>]. In controls, delivering PAS at an interstimulus interval shorter than the time needed for the somatosensory afferent response to reach the cerebral cortex leads to an excitability decrease (10 ms, PAS10), whereas using an interstimulus interval longer than the time needed to reach the cortex increases the excitability of the sensorimotor cortex (25 ms, PAS25). Using this paradigm, Pierelli *et al.* [49<sup>■</sup>] were able to show that PAS10 induced a paradoxical potentiation of MEP amplitudes in interictal MO patients, whereas healthy volunteers had physiologically reduced MEP amplitudes. Conversely, PAS25 significantly increased the cortical excitability in controls, as expected, but non-significantly enhanced MEP amplitude in MO. These results are compatible with a dysfunction of regulation of excitatory glutamatergic synapses within the sensorimotor cortex, and point to a malfunctioning of long-term depression and potentiation mechanisms in MO patients between attacks. In a subgroup of study participants, the authors observed that the more deficient the long-term PAS-induced plastic changes, the more thalamocortical activation decreased, that is, a lowered cortical preactivation would be responsible for the impaired synchronous regulation of excitatory synapses within the sensorimotor cortex. Physical activity is a well known worsening factor of migraine intensity during attack. A recent study demonstrated that magnetoencephalographic activity differed between female migraineurs and healthy volunteers when performing a motor task during an attack, with a hyperactivation of primary sensorimotor and supplementary motor cortices, which was interpreted as a sign of hyperexcitability [47]. Previous evoked potentials studies had already shown excitability changes in ictal and perictal periods [17].

In an attempt to prospectively follow women suffering from menstrual migraine during the menstrual cycle, Morlet *et al.* [53] recorded event-related potentials associated with repeated auditory stimuli applying a protocol that contained unexpected deviant stimuli: the frontal automatic mismatch negativity was measured as well as late components reflecting attention orienting. Overall, the auditory sensory processing seemed normal, but patients showed signs of increased automatic attention orienting to the sound income that were thought to be related to abnormal involvement of frontal networks. An interictal impairment of auditory cognitive processing was also recently retrieved

when analysing event-related synchronization of  $\alpha$  EEG rhythm, which in normal study participants does inhibit the tonic firing of cortical neurons. Early  $\alpha$  rhythm phase locking was significantly less delocked during the period of event-related synchronization fading in migraineurs compared with healthy volunteers. This phenomenon was interpreted as an indicator of increased top-down inhibition in migraine [55].

## CONCLUSION

The presence of a habituation deficit of visual EPs, often considered as a neurophysiological ‘hallmark’ of interictal migraine, has been questioned. Lack of blinding was pointed out as the origin of a positive expectation bias. However, some genetic, environmental or behavioural differences could exist between populations. An impaired thalamocortical drive is demonstrated in interictal phase, and may reflect disease severity, whereas it normalizes in ictal phase as well as in chronic migraine condition, where a strength enhancement of primary cortical activation is observed. Assessments of cortical excitability are overall compatible with an interictal dysexcitability, which might be of subcortical (thalamo-cortical) origin, or correspond to a primary cortical dysfunction because of an impaired inhibition (impaired regulation of excitatory glutamatergic synapses). These phenomena are not mutually exclusive: they could coexist or even occur in varying degrees depending on patients and on the point they were recorded in the migraine cycle, which may account for the heterogeneity in migraine phenotypes and electrophysiological results. Finding a reliable and reproducible electrophysiological biomarker for such a multifaceted and cycling disease as migraine still remains a challenge. Collaborations between centres and protocol standardizations would be useful.

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*Search strategy:* The literature search was performed in November 2015. Only original case-control studies performed in human and published in English within the last 2 years were considered, using the following keywords *migraine, headache, electrophysiology, neurophysiology, evoked potentials, and magnetic stimulation. Case reports, review articles, letters to editors, and articles only available in abstract form were excluded.*

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**Conflicts of interest**

*There are no conflicts of interest.*

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