Chapter 8
Neurophysiology of Migraine

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Abbreviations

BAEP	Brainstem auditory evoked potential
CAP	Cyclic alternating pattern
CM	Chronic migraine
CNV	Contingent negative variation
CR	Corneal reflex
CSP	Cortical silent period
EEG	Electroencephalography
EMG	Electromyography
ERP	Event-related potential
ES	Exteroceptive suppression
HR	H-response-increased photic driving amplitude
IDAP	Intensity-dependent auditory evoked cortical potentials
LEP	Laser evoked potential
MA	Migraine with aura

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MEP Motor evoked potentials
MO Migraine without aura
MOH Medication overuse headache
nBR Nociceptive blink reflex
NSM Non-sleep-related migraine
PAS Paired associative stimulation
PD Photic driving
PR Pattern reversal
PSG Polysomnography
PT Phosphene threshold
qEEG Quantitative electroencephalography
rTMS Repetitive transcranial magnetic stimulation
SM Sleep-related migraine
SSEP Somatosensory evoked potential
sTMS Single-pulse transcranial magnetic stimulation
TCR Trigemino-cervical reflex
tDCS Transcranial direct-current stimulation
TMS Transcranial magnetic stimulation
TSR Trigemino-spinal reflex
VEP Visual evoked potential

8.1 Introduction

Migraine is one of the most common and disabling neurological disorders. It is characterised by recurrent attacks of headache that are widely variable in duration (i.e. between 4 and 72 h), intensity and frequency and are accompanied by nausea/vomiting and/or photo-/phonophobia. In some cases, migraine attacks are preceded by, or associated with, focal neurological symptoms, i.e. aura. A proportion of episodic migraine patients experiences a progressive increase in attack frequency leading to chronic migraine (CM), defined as 15 or more headache days with eight or more migraine attacks per month. Owing to the lack of interictal sequelae after transient ictal dysfunction, migraine is commonly considered as a prototype of functional disorders of the brain.

The clinical manifestations of the more common migraine types, with and without aura, probably depend upon a complex relationship between genetic, environmental and endogenous cognitive and emotive factors, the so-called migraine susceptibility. These factors should also be studied during the interictal period to search for the underlying dysfunctions that are able to cyclically ignite migraine attacks, probably involving both neuronal and vascular components within the head. These components include the cerebral cortex, the brainstem (e.g. periaqueductal grey matter and the monoaminergic nuclei), the thalamus and the peripheral and central components of the trigemino-cervico-vascular complex. The relative importance and the exact sequence of activation of these structures during a migraine attack remain elusive and are still under extensive investigation.

Many atraumatic methods are currently available for assessing neural functions in humans, contributing to the recent advances that have been made in understanding the pathophysiological facets of migraine. These methods of clinical neurophysiology have allowed the in vivo measurement of the migraineurs' responses to the application of various cephalic or extracephalic stimuli. Several interesting changes have been reported using multimodal evoked potentials, with both noxious and innocuous stimuli, brainstem and spinal withdrawal reflexes and transcranial neuromodulatory techniques such as magnetic or direct-current stimulations. Results have suggested that neurophysiological states undergo fluctuations related either to the development of a migraine disorder, to the cyclical recurrence of attacks or to the eventual migraine chronification. Changes induced by the use or the overuse of certain pharmacological treatments have also been reported.

This evidence indicates, on the one hand, a relationship between electrophysiological changes and migraine, in spite of some remaining controversies. On the other hand, it suggests that the methodologies of clinical neurophysiology seem to be suitable for acquiring further knowledge on the generation of the migraine attack, its recurrence as well as the transition from an episodic to a chronic state. The intent of this chapter is to provide a comprehensive overview of the results provided by different neurophysiological techniques that have been used to study migraine pathophysiology.

8.2 Electroencephalography

Electroencephalography (EEG) was the first electrophysiological method used to study brain function of migraine patients. Although EEG was not recognised as useful for the diagnosis of non-acute primary headache disorders, it may provide useful information in a research setting. Researchers have observed changes regarding three major EEG features: increased photic driving (PD) amplitude to trains above 18 Hz, often called 'H-response' (HR); alpha activity abnormalities; and the presence of slowing. In addition, EEG studies have been used to investigate the still ongoing discussion about a proposed relationship between EEG and epilepsy.

Several blinded studies have shown slight excess of various EEG features in migraine (for a review of the early EEG literature, see [1]). Definitely abnormal EEG has seldom been reported: focal slowing in 0–15 % and spiking in 0.2–9 % of patients, generally rather similar to prevalences in healthy controls [2]. Consistent EEG changes during a visual aura have not been reported, although patients with brainstem aura (previously termed basilar-type migraine) may have severe clinically relevant EEG slowing that may last for several days [3–6].

During the last 50 years of publication, the increased photic driving response has rather consistently been reported in migraineurs [7]. The specificity of HR is low however, because it may also occur in healthy subjects. In a recent study by Fogang et al. [8], moderate specificity (69 %), but good sensitivity (82 %) was observed using visual EEG inspection for PD at 20 Hz in a large cohort of migraine patients,

but spectral analysis showed that visual sensitivity was considerably overestimated. A higher incidence of PD responses has been observed in patients with migraine-associated vertigo [9], as well as a positive correlation between PD and some of the clinical features of migraine, such as autonomic symptoms [10]. However, a major limitation of these studies was the inclusion of patients without taking into account the period in their migraine cycle. Bjørk et al. addressed this issue and compared recordings between attacks with those performed before, during and after an attack, as well as with the EEGs of healthy subjects in a fully blinded study [11]. PD was in fact depressed both during and between attacks in migraineurs without aura (MO), while it was increased immediately before an attack. This pattern was also related to the increased severity of symptoms [12].

Multichannel EEG during repetitive flash stimulation in MO patients who were between attacks identified phase hypersynchronisation of the alpha rhythm in all regions of the scalp, especially in migraine without aura [13]. Migraine with aura (MA) patients seem to behave differently since a distinct decrease was observed in the power of the beta frequency band compared with both migraineurs without aura and controls [13].

Quantitative electroencephalographic techniques have shown two parameters to be particularly significant in migraine: alpha activity and slowing (excess theta or delta activity). Alpha rhythm asymmetries and alpha total power abnormalities have been reported [14]. Alpha total power contralateral to the visually affected hemifield was decreased, within 3 days of an attack [15]. Alpha power was also reduced in MO on the headache side and in patients with menstrual migraine up to 24 h before the attack [15]. In some studies an increase in alpha power was observed [14, 16], while decreased alpha power was seen bilaterally in medial parts of the frontal cortex with the LORETA localisation method [17]. However, many past studies did not control for proximity to the next [14] or even the last attack [16]. In a recent blinded study, controlling for migraine phase, occipital alpha was normal interictally, while alpha rhythm variability increased in the pre-ictal phase and alpha power increased during the attack [18], suggesting that observed changes in the alpha rhythm may be caused by the temporal proximity to the next migraine attack. The changes in alpha rhythm seem to be related to increased migraine load and clinical photophobia [18].

Migraine patient groups may also have increased slow activity mostly over the temporo-occipital areas [14, 19]. An increase in theta power has been observed in all cortical regions and an increase in delta activity in the (painful) frontocentral region of adult migraineurs [18]. In another blinded paired qEEG study, these abnormalities in the frequency domain seemed to vary according to the time of examination: right before an attack (pre-ictal), during the attack (ictal) or between attacks (interictal) [20]. Interestingly, it was suggested that migraineurs are most susceptible to an attack when the anterior qEEG delta power and posterior alpha and theta asymmetry values are high [20].

8.3 Polysomnography and Sleep Dysfunction in Migraine

Migraine and sleep are connected, as sleep-related problems may act as a migraine trigger, drowsiness often precede an attack, and sleeping often relieves the attack. However, few objective polysomnographic (PSG) studies have been performed.

During the night before an attack, Göder et al. [21] found decreased cortical activation reflected by decreased number of EEG arousals and decreased REM density. Della Marca et al. [22] did also find reduced arousal index in REM and decreased cyclic alternating pattern (CAP) rate in NREM, suggesting reduced arousability interictally in patients with sleep-related migraine. In recent fully blinded and controlled studies, Engstrøm et al. [23, 24] found that patients with sleep-related migraine (attack onset during night or upon waking) had increased number of awakenings while those with non-sleep-related migraine had increased slow-wave sleep, compatible with a foregoing relative sleep deprivation. The authors hypothesised that a relative lack of sleep in non-sleep-related migraine also might explain reduced pain thresholds in this group. Thus, hypoarousal seems to characterise migraine patient groups before attacks, while the presence of nightly hyperarousal might determine if the migraineurs tend to experience attacks with nightly onset.

Using the method of nonlinear multi-electrode sleep EEG analysis, the maximum change in dimensional complexity was observed in the pre-ictal period over the scalp area where the migraine headache would subsequently be perceived [25].

8.4 Evoked Potentials

8.4.1 Visual Evoked Potentials

The amplitude of flash or pattern reversal visual evoked potentials (VEPs) was normal in the majority of studies, but in some it was increased and in others decreased compared with controls. Interhemispheric VEP amplitude asymmetry has been reported several times [26].

Amplitudes of VEPs normally decline during repeated stimulation, often referred to as habituation. Several pattern reversal VEP studies have shown an interictal habituation deficit between the first and the following blocks of responses [27–30] (see [31] for a review).

Other VEP studies have not managed to reproduce lack of habituation in migraine [32–34]. The discrepant findings may be caused by methodological differences between studies. A lack of habituation measured by VEP has not been reproduced in fully blinded studies [35]. Further studies are therefore needed in order to accept it as a reliable biomarker for migraine.

However, a lack of habituation was also recently found for visual evoked magneto-encephalographic responses [36] and motion-onset (M-VEP) visual evoked potentials [37]. Altered visual processing in migraine may be related to short-range lateral inhibition in the visual cortex [38], and it is possibly under abnormal thalamic and thalamocortical control [39]. In fact, experimental paradigms able to positively modulate thalamocortical activity, such as 3-min hyperventilation [40] and 1-h light deprivation [41], have re-established interictal VEP habituation. Finally, the degree of habituation may depend on where patients are in the migraine cycle, since some cross-sectional studies indicated that VEP habituation is minimal between attacks and more prominent during an attack [38, 42, 43]. However, this was not confirmed in a longitudinal blinded study [44].

8.4.2 Auditory Evoked Potentials

In the majority of studies, researchers were not able to find interictal abnormalities in the baseline parameters of short-latency brainstem auditory evoked potentials (BAEP). Sand et al. [45] provide a review of older BAEP studies in their Table 5. Similar to the results of VEP studies, a significant increase in side asymmetries has been reported for BAEP [46]. A lack of habituation of waves IV–V dispersion was found in migraineurs to 40 dB clicks (but not to 55 and 70 dB clicks) in a longitudinal blinded study, in which a direct relationship between BAEP amplitudes and blood 5HT levels was also reported in controls, but not in migraineurs [45]. A lack of habituation has also been reported for cortical auditory evoked responses for 70 dB, but not 40 dB stimuli [47].

Stronger stimulus intensity dependence of auditory evoked cortical potentials (IDAP) was found between attacks in migraine sufferers compared with control subjects in one study [47]. This may be another feature of lack of habituation, as another study reported a negative correlation between amplitude habituation and IDAP [48]. In common with VEP, IDAP has been reported to normalise during an attack [42]. One study, however, did not confirm this phenomenon [33].

Evidence that the thalamus in migraine abnormally controls the cortex between attacks is further supported by analysis of sensory gating, defined as a filtering of external stimuli by central sensory pathways, in which the thalamus seems to play a major role. In an auditory P50 event-related potential (ERP) paradigm, sensory gating was markedly reduced in migraine patients compared with controls [49, 50], probably in a way that is related to reduced short-term habituation.

8.4.3 Somatosensory Evoked Potentials

The amplitude and latency of standard somatosensory evoked potentials (SSEPs) after median nerve stimulation were normal between attacks in the majority of studies, although increases in amplitude were reported in the only study that used magnetoencephalography [26]. During a hemiparaesthetic migraine aura, the parietal N20 SSEP component was significantly delayed and reduced in amplitude, and both anomalies progressively returned to values within the normal range during the following headache phase [51].

In concordance with VEP and BAEP studies, a significant increase has been observed in interhemispheric asymmetries for the amplitude of the N30 SSEP component [52]. Deficient habituation has also been confirmed interictally for the SSEP components. In fact, both the cervical N13 [53] and the sensorimotor N20 [53–55] component have shown an increasing, instead of a decreasing, response during continuous electric stimulus repetition.

The application of a specific bandpass digital filter to broadband SSEP recordings permits the extraction of a series of high-frequency oscillations (HFOs). Multichannel source localisation analyses and pharmacological manipulation studies have shown that the separate analysis of the early (before N20 peak) and late (after N20 peak) HFO components enables the measurement of thalamocortical fibre activity and primary cortical activation, respectively. Between attacks, the early component of the HFOs, but not the late component, was significantly smaller in migraineurs [55–58], and this reduction was associated with a worsening in the clinical evolution of migraine [59].

8.4.4 Event-Related Potentials and P300

Contingent negative variation (CNV) is a long-latency EEG surface negative potential with cognitive and motor components and is considered to be an index of cortical arousal during orientation and attention. Two groups have consistently found increased CNV amplitude interictally in migraine, which is more pronounced for the early component (iCNV). The iCNV component seems to be enhanced during stress and the premenstrual phase of the ovarian cycle, but not during pregnancy [26, 60]. These iCNV changes correlated inversely with disorder duration [61], while the late component of CNV correlated inversely with depressive symptoms [62].

In concordance with some studies of VEPs, AEPs and SSEPs, CNV have showed a lack of habituation between attacks [63, 64]. This abnormal information processing has been observed only for the early and not for the late CNV component [64–67]. This phenomenon seems to have familial characteristics [68], increase just before an attack. Habituation seems to normalise during an attack [65, 68], after drug treatment [69, 70] and after non-pharmacological interventions [71].

A loss of habituation in migraine has also been described for cognitive functions, as measured by the event-related P300 potential. This was seen interictally using a visual or auditory oddball paradigm and was found to correlate inversely with platelet 5HT content [26]. However, the habituation deficit could not be confirmed in a recent study on menstrual migraine patients [72]. In addition, several authors, including the latter, did not control for proximity to the next attack.

8.4.5 Pain-Related Evoked Potentials

A reliable and objective way to study nociceptive evoked brain responses in the trigeminal or extracranial systems is by using brief laser pulses, which are able to excite Aδ and C nociceptors in the superficial skin layers.

Between migraine attacks, the N2-P2 laser evoked potential (LEP) is normal after cephalic and extracephalic stimulation. Remote heterotopic capsaicin application [73] as well as a distraction task [74] reduced LEP amplitude in healthy subjects,

but not in migraineurs, probably because of defective brainstem inhibitory control. In migraine, the N2-P2 amplitude increased during the premenstrual phase [75], whereas it is decreased after interfering stimulation by images with different affective content [76], after excitability-enhancing 5 Hz-repetitive transcranial magnetic stimulation (rTMS) [77] and after visual and verbal suggestion, especially in patients with more severe migraine [78]. Moreover, LEP amplitudes increased [79], and their distribution was shifted rostrally during an attack in one study [80].

LEP studies have confirmed that the reduced habituation seen during repetitive stimulation between migraine attacks also can be found for the noxious stimulus modality during short [81] as well as long periods of painful stimulation [82]. Moreover, a lack of habituation of LEP amplitude has been found in patients for both cephalic (supraorbital zone) and extracephalic (hand dorsum) stimulation [82]. Interestingly, a persistent lack of LEP N2-P2 habituation was observed during an attack [82], which contrasts with the response normalisation found by some authors with non-noxious EPs and in the premenstrual phase [75].

8.5 Neuromodulation Methods

8.5.1 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive method used to study the excitability of the underlying cortical area. Both single-pulse TMS (sTMS) and repetitive rTMS have been performed in migraine studies, the latter capable of durably modifying the excitability of the stimulated cortical area.

8.5.1.1 Single-Pulse TMS

With sTMS, both phosphene thresholds (PT) and motor thresholds have been assessed in migraine but with discrepant results. sTMS has the advantage of relying on an objective measure, the amplitude of motor evoked potential (MEP) recorded from a muscle. Briefly, both increased and decreased thresholds for MEP have been reported in migraineurs. However, most studies found no significant differences compared to controls [83, 84]. MEP thresholds were significantly increased in migraine after light deprivation, an experimental way to modulate subcortical and cortical activities, whereas they remained stable in controls [84]. Using paired TMS pulses, intracortical facilitation was found in one study [85], but not in another [83]. The cortical silent period was normal [85, 86] or reduced [87, 88] in the interictal period of episodic migraine. Cerebellar conditioning TMS showed a significant reduction in cerebellar inhibition on the motor cortex in migraine patients compared with controls [89].

With sTMS over the visual cortex, both decreased [86, 90] and increased [91] PT have been reported in migraine. Several studies also found no differences compared to controls [92, 93]. A recent meta-analysis found decreased PTs in migraineurs

with aura interictally, but it was emphasised that the results of PT studies varied greatly because of methodological differences and that their results therefore should be interpreted with caution [94].

8.5.1.2 Repetitive Transcranial Magnetic Stimulation

Studies using repetitive transcranial magnetic stimulation (rTMS) have reported abnormal cortical excitability, manifesting as paradoxical effects, in response to both depressing and enhancing rTMS paradigms, particularly in MA. Brighina and coworkers observed that 1 Hz-rTMS at 90 % of the RMT over the motor cortex of MA patients significantly activates rather than inhibits intracortical facilitatory circuits [95]. More recently, two independent research groups provided evidence that 5 Hz-rTMS over the motor cortex induced short-term synaptic potentiation more easily in MA patients than those without aura and controls, in whom they did not find significant variations in MEP size [96, 97]. On the other hand, excitatory 5 Hz-rTMS induced a significant decrease in MEP size in MA patients rather than the clear MEP facilitation seen in controls [97]. The authors interpreted these paradoxical responses as being due to a compensatory cortical homeostatic metaplastic mechanism in response to a forced increase in cortical excitability. Consistent with evidence from several EP studies, the MEP response to 5 Hz-rTMS strongly depends on when patients are studied during the migraine cycle and on attack frequency [98]. In MO patients, Pierelli et al. [99] used a paired associative stimulation (PAS) paradigm, a protocol coupling a peripheral nerve and cortical TMS in order to study long-term associative learning mechanisms. The authors found that (the presumably inhibiting) PAS paradigm paradoxically increased MEP amplitudes, while the enhancing part of the PAS protocol did not induce potentiation [99]. More interestingly, the same authors observed in a subgroup that the PAS-induced plastic changes were inversely related to thalamocortical activation, as assessed by early somatosensory HFOs, suggesting a possible explanation for the observed paradoxical effects.

8.5.1.3 Transcranial Direct-Current Stimulation

Transcranial direct-current stimulation (tDCS) is another non-invasive method that can modify the excitability of the underlying cortex: cathodal tDCS is inhibitory and anodal tDCS excitatory. Chadaide et al. [92] studied the effect of tDCS on TMS-elicited phosphene thresholds (PT). While baseline PTs and the anodal tDCS-induced PT decrease were similar between migraine patients and control subjects, cathodal stimulation, that increased the PT in healthy subjects, did not affect the patient group. In accordance with the latter paper, Siniatchkin et al. [100] showed that VEP amplitude can increase under anodal and decrease under cathodal tDCS in healthy subjects, while neither affected VEPs in MA patients. Viganò et al. reported *that* N1-P1 and P1-N2 VEP amplitude habituations increased immediately after anodal tDCS applied over the visual area in migraineurs and controls [101]. Cathodal

tDCS, but not anodal tDCS, restored the normal facilitatory response to 5 Hz-rTMS trains in MO and MA patients, as both groups showed a paradoxically inhibited response at baseline [98].

8.6 Electromyographic (EMG)-Recorded Reflexes

8.6.1 Brainstem Reflexes

Several research groups have reported that the exteroceptive suppression (ES) of temporalis muscle activity is unchanged between attacks in patients with migraine in comparison with controls, particularly the multisynaptic ES2 and its recovery curve, which are markers of the excitability of interneuronal networks in the ponto-medullary reticular formation [102].

The conventional blink reflex is used to explore the trigeminal system and has produced inconsistent results. Some studies have reported normal values for R1 and R2 latencies and amplitudes [103, 104], whereas some have found increased R2 latency during the pain-free period [105], and others have found lower values of R2 amplitude and size only during the headache phase of migraine, which returned to the normal range after sumatriptan injection [106]. Opposite results have been obtained from analysis of the BR recovery curve after supraorbital conditioning, since it was reported to be normal in one study [102] and slightly faster in another [107], especially when patients report allodynia during migraine [108].

Using a stimulation electrode that mainly activates Aδ-fibres, Katsarava et al. [109] found normal latencies and areas under the curve for the nociceptive blink reflex (nBR) R2 component in migraineurs interictally, but reduced habituation, as another group observed in a later study [110]. During the migraine attack, nBR-R2 amplitude and habituation were shown to be increased [109, 111, 112], which suggests temporary ictal sensitisation of the reflex pathway. Recovery curves for the nBR-R2 component both after supraorbital or peripheral conditioning were within normal limits between migraine attacks [113].

In a study of the corneal reflex (CR), which is mediated by small nociceptive fibres, a lower reflex threshold was found between attacks in migraineurs compared with controls [114]. This contrasts with the results of a subsequent study where baseline response areas under the curve and latencies of the CR- R2 components did not reach the level of significance [115].

Knowing that the trigeminal pathways and motor neurons in both the neck and upper limb muscles are functionally and anatomically connected, neurophysiological abnormalities in the pain-free phase have been similarly revealed by means of trigemino-cervical reflex (TCR) recordings [116], but no significant differences were observed for the trigemino-spinal reflex (TSR) [117]. Between attacks, the recovery cycle for the TCRs was markedly faster in migraine patients than in controls, while no significant differences were observed for the TSRs. A cold pressor stimulus reduced the TCR and TSR areas equally in both migraine patients and controls [117].

8.6.2 Spinal Reflexes

Within the nervous system, one of the most typical abnormalities resulting from dysfunction of pain processing is represented by activity-dependent changes in the excitability of central neurons resulting in an abnormal temporal summation (TS) of pain stimuli. In humans, the functional activity of the TS of pain can be tested using the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR) method.

An increased NWR area with a normal reflex threshold has been reported in episodic migraine between attacks. A reduced TST of pain [118], accompanied by an increase in pain perception [119], was demonstrated in episodic migraine in between attacks. Interestingly, administration of a nitric oxide donor, glyceryl trinitrate, induced a transitory facilitation of TS-NWR only in those patients who developed a full-blown migraine attack [120].

8.7 Chronic Migraine

Some migraine patients experience a progressive increase in attack frequency, leading to headache chronification, i.e. they have 15 or more headache days per month with eight or more migraine attacks per month. The majority of these patients have CM, mostly associated with the excessive intake of acute medications, defining medication overuse headache (MOH). The precise pathophysiological mechanisms are not yet understood. Among various possible explanations, central sensitisation and defective central pain control systems are the most widely accepted causative factors.

An increase in the amplitude of pain-related cortical responses has been detected in chronic migraine both with [121] and without medication overuse [122]. Similar to the situation during an attack, the LEP brain distribution is shifted rostrally within the anterior cingulate cortex in CM [123].

Excessive cortical activation has also been reported in non-painful SSEP studies of CM or MOH [54, 58].

In CM, a neurophysiological pattern quite similar to that of episodic migraineurs recorded during an attack, including habituation, ictal thalamocortical activity (early HFO) normalisation and increased amplitude of the primary cortical component (late HFOs) [58].

In MOH, the initially higher SSEP amplitudes that reflect sensitisation were further increased during stimulus repetition, resulting in a persistent sensitisation proportional to the duration of the headache chronification phase [54]. In addition, SSEP amplitudes may differ according to the overused drug, being smaller in triptan overusers than in patients overusing nonsteroidal anti-inflammatory drugs (NSAIDs) [54]. These abnormalities in the cortical responses to somatosensory stimulation seem to be influenced by genetic factors [124]. Moreover, MOH patients still showed deficient habituation mechanisms during CNV [125] and LEP [126]

recordings, the latter normalising after withdrawal of the overused medication. In agreement with the SSEP study mentioned above [54, 58], and as usually happens during an attack, the VEP P100m amplitude habituated normally on stimulus repetition in CM and in controls [36].

Using a test of cortical inhibition known as transcranial magnetic suppression of perceptual accuracy, researchers observed that CM patients (with or without medication overuse) had the lowest suppression index in comparison with healthy controls, with episodic migraineurs falling in between [127].

By further exploring inhibitory circuits, Currà et al. measured the TMS-induced cortical silent period (CSP) in a group of MOH patients. CSP duration was significantly shorter in triptan overusers than in the NSAID or triptan-plus-NSAID overuser subgroups [88]. Cosentino et al. reported an inhibitory response in CM patients during trains of TMS at 5 Hz, instead of a progressive facilitation, similar to results obtained by the same researchers during an attack of episodic migraine [98].

In CM, sensitisation phenomena might manifest either at the brainstem [128] or spinal levels. A significantly lower withdrawal reflex threshold, higher amplitude and lower TST were found in MOH patients before detoxification in comparison with episodic migraine and controls [118]. All these neurophysiological abnormalities tended to improve after a detoxification programme [118].

8.8 Conclusions

The diagnosis of migraine is still based on medical interviews and an objective neurological examination, while paraclinical tests mainly are useful to exclude secondary headache and to evaluate comorbid disorders or severe hemiplegic or brainstem aura [129]. The search for biomarkers that may predispose individuals to recurrent migraine attacks has provided a range of interesting bioelectrical parameters that correlate with migraine and seem to change during the migraine cycle on the group level. Notably, many neurophysiological studies have disclosed changes in the spinal, brainstem and cortical responsivity to external innocuous or noxious stimuli in migraine. These results can be summarised as follows (Table 8.1):

- Enhanced interictal photic driving in EEG seemed to be rather consistently reported, but this ‘H-response’ is not specific, and it was not confirmed in a fully blinded study.
- EEG power mapping (qEEG) studies have shown variable changes in two parameters alpha activity and excess slowing, but the influence of unspecific factors, like drowsiness, has not been settled.
- In EP studies of episodic migraine, a lack of habituation on recordings performed between attacks and sensitisation during the attack have been found, especially with somatosensory stimuli. Habituation tends to normalise during attacks. In the pre-ictal phase, both sensitisation and deficient habituation may variably co-exist in response to non-noxious and painful stimuli. In patients who evolve into CM, the cortical response pattern could be locked in a state combining both initial sensitisation and late habituation. The usability of VEP habituation as a neurophysiological biomarker in migraine is limited by the lack of replication in fully blinded VEP studies.

Table 8.1 Synoptic table of electrophysiological changes comparing episodic migraine between attacks, during an attack and chronic migraine with or without medication overuse

	Episodic migraine between attacks	Episodic migraine before or during an attack	Chronic migraine/MOH
Technique			
EMG-recorded reflexes	↓ Habituation of BR	Normal habituation	Persistent sensitisation at the trigeminal and spinal level
	↑ Recovery cycle of TCR	Transient sensitisation	
EEG	Normal or increased photic driving. Increased alpha variability and excess slowing	EEG activity changes shortly before and during the attack. Increased photic driving before attack	
PSG	↓ Arousals in NSM and preserved arousability in SM	↓ Arousals before attack in SM	
		↓ Sleep latency before attack	
TMS and tDCS	Paradoxical effects	Changes shortly before, during and immediately after the attack	Paradoxical prevalence of inhibitory responses
EP and ERP	↓ Thalamocortical activity	Normal thalamocortical activity	Normal thalamocortical activity
	Normal or ↓ habituation	Normal habituation or transient sensitisation	Normal (CM) or ↓ habituation (MOH)
			Persistent sensitisation

Arrows indicate the direction of change
CM chronic migraine, *EEG* electroencephalography, *EMG* electromyography, *EP*, evoked potentials (visual, sensory and auditory), *ERP* event-related potentials, *MOH* medication overuse headache, *TMS* transcranial magnetic stimulation, *tDCS* transcranial direct-current stimulation, *PSG* polysomnography, *SM* sleep-related migraine, *NSM* non-sleep-related migraine

- Only subtle abnormalities in the processing of noxious information have been revealed between migraine attacks, while more prominent changes seem to occur during an attack and when migraine becomes chronic.
- Studies with rTMS or tDCS have reported abnormal cortical excitability manifesting as paradoxical effects in response to both depressing and enhancing paradigms, particularly in MA. These paradoxical effects might be a consequence of an abnormal thalamocortical drive that impairs short- and longer-term changes in cortical synaptic effectivity, finally leading to maladaptive responses.
- Studies with EEG and visual and somatosensory evoked high-frequency oscillations suggest that an abnormal rhythmic activity between thalamus and cortex, namely, thalamocortical dysrhythmia, may be the pathophysiological mechanism underlying abnormal information processing in migraine.

Future research in this subject area in oncoming years should be devoted to understand the precise anatomical structures involved in the recurrence of migraine susceptibility and to the development of new target pharmacological and non-pharmacological interventions that are able to improve temporal information processing.

In order to reduce divergences between studies, more attention should be paid to performing blind studies. In confirmatory research, blinding both

recording and analysis would be helpful. Accurate clinical data and a headache diary should be recorded before, during and after the day of testing, in order to prospectively monitor the patients' clinical fluctuations. The effects of homeostatic factors including sleep, arousal, attention and drowsiness should be explored, both with polysomnographic studies and more sophisticated ERP protocols.

Better insight into the nature of interictal cortical dysfunction will hopefully enable us to solve the mystery of migraine recurrence, a phenomenon so enthralling that the writer Oliver Sacks considered it to be 'not only an elemental activity of the cerebral cortex, but an entire self-organising system, a universal behaviour, at work….the creative heart of Nature itself' [130].

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