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Neurophysiology of the Migraine Brain

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Headache

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Gianluca Coppola • Wei-Ta Chen
Editors

Neurophysiology of the Migraine Brain

Springer

Editors
Gianluca Coppola
Department of Medico-Surgical Sciences
and Biotechnologies
Sapienza University of Rome
Latina, Roma, Italy

Wei-Ta Chen
Neurological Institute
Taipei Veterans General Hospital
Taipei, Taiwan

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Foreword

In the past decades, neurophysiology has had an extremely important role in the study of headache disorder pathophysiology. Following this line, researchers have defined through the years new noninvasive methodologies that have produced great results in the comprehension of migraine mechanisms and in their correlation with different neuroimaging and clinical subsets.

Neurophysiology has explored the migraine brain in vivo, bringing to the definition of the migraine disease as a "biobehavioral organic maladaptive central pain."

This book *Neurophysiology of the Migraine Brain*, as the 12th volume of the Headache Series, completes the landscape of this editorial project, covering an important research area that must be known by all those who approach primary headaches also from a clinical point of view.

Department of Clinical and Molecular Medicine
Sapienza University,
Rome, Italy

Paolo Martelletti

Preface

About one in every five patients referred to the neurologist suffers from headache; the majority have migraine. Although headache specialists understand migraine clinically, the pathophysiological changes which provoke and accompany the development of a migraine attack have still been debated.

Several decades passed since the pioneering electroencephalographic study of Golla and Winter (1959), emphasizing abnormal rhythmic activities in migraine. Since then, rapid advances in the field ensued. An enormous amount of neurophysiological studies has enriched our understanding of the pathophysiology facets of the migraine pathology. Almost all the known techniques of clinical electrophysiology were used to study the migraine brain, and more recently, new neurophysiological tools have energized it. Nevertheless, the application of the principles of peripheral and central neuromodulation is a promising way to transfer the principles of synaptic plasticity to the patient's bedside.

The Neurophysiology of the Migraine Brain book is part of the *Headache Series* book endorsed by the European Headache Federation and is the first attempting to summarize the state of the art in the field. We were delighted to work with the internationally recognized experts in their respective fields of research. The various chapters of the book cover all the aspects of clinical neurophysiological methods that make significant advances in the understanding of the pathophysiology of migraine.

We hope that the present book will be not only useful for the beginners but also a reference for the experts.

Rome, Italy — Gianluca Coppola
Taipei, Taiwan — Wei-Ta Chen

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Chapter 1
Electroencephalography in Migraine

Trond Sand, Petter Moe Omland, and Shuu-Jiun Wang

1.1 Introduction

Electroencephalography (EEG) is the oldest, most well-known, and probably the most useful electrophysiology method for the brain in clinical neurology. From its discovery by Hans Berger, published in 1929, it has been applied to and studied in a variety of conditions, and its role in epilepsy and coma is undisputed. The essence of EEG is the ability to record cortical and thalamocortical rhythmicity, the most well-known being the posterior dominant "alpha" rhythm (8–13 Hz in adults), and 12–16 Hz "sleep spindles" [1]. In healthy subjects, EEG defines the brain's electrophysiological signature of sleep stages and arousals, while characteristic spike waves suggest epilepsy, and various patterns of slower theta (4–7 Hz) and delta (<4 Hz) waves suggest either sleep or a disease within the brain. Higher frequency beta (14–30 Hz) and gamma (31–80–150 Hz) rhythms have more recently been ascribed important roles in memory and learning [2], and faster "ripples" recorded intracranially seem to be important markers for epileptic seizures in several patients [3].

The recording and interpretation of EEGs require considerable expertise and experience since biologic and technical artifacts (like muscle activity and movements) and spiky normal variants (prominent in drowsiness) must be identified to

T. Sand (✉) · P. M. Omland
Department of Neuromedicine and Movement Science, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway
e-mail: trond.sand@ntnu.no

S.-J. Wang
Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

Brain Research Center and School of Medicine, National Yang-Ming University, Taipei, Taiwan

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avoid overinterpretation. Thus, a visual analysis of EEG must be done to identify specific abnormal EEG elements, like spike waves or triphasic delta waves, and normal elements, like the alpha and mu rhythms or the "rhythmic temporal theta of drowsiness." However, other "automated" or "quantitative" methods have been developed to measure the amount or magnitude of various EEG rhythms [4, 5]. Such methods, often classified under the "QEEG" (quantitative EEG) umbrella, are very useful in migraine research. The most common method is spectral (frequency) quantification by the fast Fourier transform (FFT) or wavelet transform (WT). Another related method is EEG coherence, which is used to assess the degree of connectivity between brain regions.

The recording of CNS responses to sensory or cognitive stimuli or tasks also depends on our ability to discern very small responses from the ongoing EEG using techniques like averaging (for evoked potentials in the time-amplitude domain) or by the use of either event-related synchronization and desynchronization (ERS/ERD) or other spectral quantification algorithms in the time-frequency domain.

1.2 Clinical Use of EEG in Migraine

Early attempts to use EEG in migraine patients were often limited by methodological problems, like lack of blinding and unclear definitions of "abnormality." In a comprehensive critical review of the older literature by Sand [6], it was also noted that very few studies had been adequately blinded. However, data from two adult and two children blinded studies suggested that EEG rhythmicity could be slightly changed among migraine patients, while clear-cut abnormalities, like focal slowing or spikes, seemed to be equally rare among patients and controls. Consistent EEG changes during visual aura have not been reported, but EEG slowing is common during hemiplegic migraine attacks and during the subtype of brainstem aura with disturbed consciousness ("basilar migraine").

For many years it has been speculated that there is a link between migraine and epilepsy. A typical migraine attack may possibly trigger an epileptic seizure [7, 8], and "migraine-aura triggered seizure" is included in ICHD-3 (code 1.4.4) (Headache Classification [9]). Migraine-like symptoms and epilepsy may also coexist in mitochondrial encephalopathy [10]. However, a proposed link between partial childhood epilepsy and migraine [11] could not be confirmed by Santucci et al. [12]. A migraine-like headache may rarely be one of the symptoms during (or after) a complex partial seizure [13, 14], and children with one of the occipital epilepsy types may also report headache during an attack [15]. However, so-called migralepsy may just be epileptic visual auras [16]. Migralepsy, renamed "ictal epileptic headache" (code 7.6.1) and "postictal headache" (code 7.6.2), remains an entity in the ICHD-3 [9], although its detailed characteristics remain unclear [17, 18].

Two European Federation of the Neurological Societies reviews [19, 20] concluded that a clinical EEG is indicated only for basilar or hemiplegic migraine and for epilepsy-related headache, since the proposed association seems to be mainly

caused by comorbidity (i.e., epilepsy with headache or migraine-like symptoms as attack-related symptoms). Hence, both EEG and MRI should be performed in many patients with atypical migraine-like acute headache attack, in order to diagnose, for example, an epilepsy syndrome or an intracranial pathologic process.

1.3 Quantitative EEG Methods

Early QEEG studies reviewed by Sand [21] found that results were not quite consistent, but a pattern of increased alpha rhythm variability and/or asymmetry was generally reported in the headache-free phase, although slowing and decreased alpha also were reported [21]. Clemens et al. [22] also reported reduced alpha power mostly in the right occipital region, while a depth source method (LORETA) suggested increased alpha in pre-cuneus and posterior middle temporal gyrus in the right hemisphere and decreased alpha bilaterally in the medial frontal cortex. Hence, increased EEG-rhythm variability among migraineurs is suggested, but methods and results have varied. Hence, the results in these early nonblinded QEEG studies could not be easily interpreted and have generally not been confirmed by independent investigators in a few fully blinded studies (see below).

More complex QEEG methods have also been applied to investigate EEG connectivity in migraine. Cao et al. [23] found reduced EEG coherence in the interictal phase of 50 migraine patients without aura, while connectivity was increased in the fronto-occipital network. Cao et al. [24], in a large longitudinal nonblinded study of 40 migraine-without-aura (MO) patients, also reported reduced prefrontal multiscale fuzzy entropy in interictal migraine and normalization in the preictal phase. Synchronization entropy (SE) and Granger causality (GC) analysis has been applied to EEG before, during, and after painful laser stimuli, suggesting increased anticipation of pain (and increased poststimulus connectivity) in MO compared to controls [25], while various differences between MO and migraine with aura (MA) patients interictally were observed during 9–27 Hz flashes [26] and pattern reversal photic stimulation [27]. Connectivity changes have also been reported with magnetoencephalography (MEG) [28]. The number of patients were rather few in some of these studies, many variables were included, and the complexity of the mathematical methods is substantial, so it is a definite need for replication by larger fully blinded studies [29] and further development of these types of interesting methods.

1.4 Magnetoencephalography

MEG is a powerful, although expensive, technique to record the magnetic counterpart of the EEG signal, sensitive to sources within cortical sulci [30]. MEG can also be used for evoked potentials [31]. Spreading depression may possibly be detectable with MEG, as cyclic direct current (DC) shifts have been recorded in a blinded

MEG study [32]. Alpha desynchronization during aura has been reported in a single patient [33]. However, identification and elimination of artifacts represent a major challenge in MEG research [34]. More recently, Li et al. [35] found increased gamma activity in left frontal and temporal regions in interictal migraine. Xiang et al. [36] reported increased heterogeneity in migraineurs between the auditory and motor tasks for higher frequencies above 100 Hz. However, it should be noted that surface-recorded fast activity, like gamma activities, can be contaminated by 50–60 Hz power-source artifacts and muscle artifacts [37].

1.5 EEG in the Period Preceding Migraine Attacks

In the last decades, it has become increasingly evident that detailed headache diaries are needed to reliably study migraine in the preictal (prodromal) and postictal phases in addition to interictal and ictal phases [38, 39]. Hence, an improved method using blinded recording, blinded analysis, and a paired design was developed [40]. EEG was repeated three times (6- to 7-day intervals) in 40 migraine patients (nine with aura) and 30 controls. More slow EEG activity was found over the frontal region 36 h before the attack starts [40]. Also, more unstable alpha and increased side difference in EEG 36 h before attack, more variable alpha rhythm 72 h before the attack, as well as increased alpha band power and peak power during the attack were found [40]. Similar findings had been reported in a group of patients with aura [38]. Cao et al. [23] also found higher EEG power in the preictal phase in a longitudinal study.

A reduced preictal cortical or thalamocortical "preactivation" may possibly explain such slowing and variability. Interictally, Bjørk et al. [41, 42] found increased theta in migraineurs, while delta correlated with headache intensity. In general, EEG power values increased toward the attack. In contrast, a recent ambulatory EEG study using self-affixed frontal EEG electrodes reported reduced frontal delta and increased beta before the attack, but technical EEG details were too sparse to evaluate its relevance [43]. The combined findings by Bjørk et al. [44] in three studies suggest rather low and variable cortical activation level before the attack. A cortical and/or subcortical fluctuating dysfunction, possibly related to thalamocortical instability (or "dysrhythmia"), may accordingly also be important in the migraine attack initiation [6, 45], as hypothesized for other painful conditions [46].

1.6 Event-Related Changes in EEG Rhythms

EEG rhythms often change by stimulation, for example, the well-known alpha suppression by eye opening and mu rhythm suppression by contralateral movement. The EEG responses to stimulations are also, and more commonly, investigated by conventional averaging [47], but only time-frequency methods will be considered briefly within the present review.

Intermittent photic stimulation (IPS) is a part of routine EEG because it may trigger epileptiform spikes in epilepsy patients. In addition, the amplitude of the evoked

photic driving at 18 Hz and above (named "H-response") over the occipital cortex can be measured by various, often FFT-based, methods. Early nonblinded and uncontrolled studies, reviewed by Sand [6] and Bjørk et al. [48], and some blinded studies [49] found increased H-response in migraine, but also in tension-type headache (TTH), head injury, and epilepsy. However, a more recent study with standard IPS and blinded recording and analysis could not confirm this finding [48]. In fact, 18 and 24 Hz driving power was considerably lower in interictal patients without aura than in controls. Most previous studies were nonblinded and did not control for preictal recordings. Hence, the presumed specific H-response abnormality in migraine, using standard IPS, is accordingly unconfirmed in a blinded controlled study.

However, a variety of method details like train duration and intensity [48] can affect photic driving, and a new short-lasting "chirp" train (minimizing habituation effects) was recently claimed to evoke increased 19–26 Hz power among 11 truly interictal migraineurs, in an open unconfirmed study [50]. EEG complexity, quantified by a new inherent fuzzy entropy method, seemed to differ between interictal and preictal phases [51]. Repetitive 8 Hz circular checkerboard reversals evoked a steady-state EEG response in primary visual cortex area 17 (cuneus) that was significantly greater in interictal migraine patients than in controls [52]. The latter study used 60 EEG electrodes and advanced time-frequency EEG processing, including source localization by eLORETA. Increased coupling to premotor, anterior cingulate, and temporal pole areas was also found [52].

Alpha1 (7.5–9.5 Hz) power is also depressed by ischemic pain in controls [53, 54], while trigeminal pain increased theta and decreased alpha activity [52]. Even nonpainful ischemic stress decreased alpha1 power diffusely in 19 migraine patients (15 without aura) compared to controls in a nonblinded study uncontrolled for preictality [54]. Deficient beta predictability after trigeminal laser pain in interictal migraine was interpreted as inadequate cortical reactivity by de Tommaso et al. [55]. However, effects of nasal trigeminal pain on theta and alpha were similar in a recent study of 30 interictal patients compared to 30 controls [52].

Gamma-band oscillations have also been suggested to reflect pain after phasic [56] and tonic [57] heat stimulation in healthy subjects. However, it is very difficult to record evoked gamma activity with scalp EEG [58]. Pain-related gamma seems to be contaminated by electromyography (EMG) artifacts [59]. A shielded room, battery-powered amplifiers [60], or computational removal of 50 or 60 Hz power-source contamination are needed. One study reports on visually evoked gamma activity in migraine patients, but results are difficult to interpret because artifact correction was not applied [61].

ERS/ERD [62] is a related powerful technique to identify how EEG rhythms are increased (synchronized) or depressed (desynchronized) after various stimuli, mainly related to movements. Mykland et al. [63] recently studied beta (12–19 Hz) ERD, representing cortical excitability during sensory processing and post-movement beta synchronization (PMBS), which represents post-stimulation cortical inhibition [64]. In the preictal phase, baseline beta power and beta ERD in contralateral sensorimotor cortex were significantly increased. PMBS, on the other hand, tended to be increased at the ipsilateral side. In the ictal phase the baseline beta activity was significantly increased, and PMBS was significantly decreased in the ipsilateral sensorimotor cortex. The results support the theory of underlying cortical hyperresponsivity in migraine, interictally contained by inhibitory control Table 1.1.

Table 1.1 Summary of results, interpretation, limitations, and suggestions for future research strategies for EEG in migraine

Method	Results	Interpretation	Limitations	Future utility
Standard resting or sleep-deprived EEG (visual interpretation)	Mostly normal or normal variants. No spikes. Slight slowing, excessive HV response	Increased drowsiness, variable attention/arousal, possible midbrain/thalamic instability?	Observer-dependent visual interpretation	Use EEG for differential diagnoses (epilepsy, intracranial pathology, encephalitis). Can be used during or after hemiplegic and brainstem aura attacks with confusion
Resting QEEG[a] (spectral/source models)	Increased alpha rhythm variability/asymmetry. Slight theta/delta increase	Thalamocortical dysrhythmia?	Small studies, variable methods, lack of validation	Define a limited set of standards for future studies (for recording, computation, statistics) Perform independent replication studies
Phase-related longitudinal in-patient EEG	Preictal slowing and increased alpha-rhythm variability in blind studies	Increased thalamocortical instability or reduced arousal before the attack	Demanding and costly studies with multiple lab visits. Interventions can be studied only interictally	Reliable ambulatory long-term EEG monitoring is needed. Could be combined with daily recording of CNS responsivity and pain sensitivity
EEG connectivity	Variable (increased or decreased with preictal normalization)	Variable	No standard. A variety of methods with many computational alternatives	Define a set of promising standards. Perform larger studies with independent test and replication samples. Perform blinded parallel imaging studies
Magnetoencephalography (MEG)	Aura can occasionally be recorded	Suggested to record spreading depressions (SD) in migraine	Lack of availability. High cost. Record spontaneous attacks only by chance	Ideal for induced migraine attacks and GBO[b] recording. Needs independent confirmation. Validation of the "MEG-SD signature" is needed

Intermittent photic stimulation (IPS)	H response[c] not confirmed in a fully blinded study. Increased SSVEP to patterned stimuli	Hyperresponsivity of occipital cortex (stimulus type-dependent)	No standard (apart from IPS in routine EEG). A variety of methods with many computational alternatives	Define a limited set of (promising) standards for future studies. Perform independent replication studies
Tonic pain (ischemic)	EEG alpha and beta attenuation in migraine and healthy controls	Increased EEG reactivity to nonpainful ischemic stress in migraine	EEG is sensitive to attention, emotion, and cognition. Many rhythms are not expressed in all subjects	Limited so far. Lack useful specific EEG markers of pain network/ matrix activation
Phasic pain (laser, nasal ammonia, electrical)	Few studies, normal or changed reactivity	Variable. Limited data so far. May reflect top-down pain control mechanisms. Beta ERD/ERS and GBO[b] can be studied	Large variety of possible tasks. Needs to control for effects of salience, affect, and cognition	More studies on well-defined different types of pain stimuli are needed. Source reconstruction (SI, SII, insula, gyrus cinguli) in various frequencies to different specific pains could be useful
Movement (ERD/ERS)[d]	Few studies on beta ERD and PMBS.[e] Increased baseline beta power and beta ERD preictally	Cortical hyperresponsivity, interictally contained by inhibitory control	Variety of possible tasks. Individual frequency-specific reactivity	Define a promising set of method standards for future replication studies. Can be combined with TMS measures of CNS excitability

[a]Quantitative EEG
[b]Gamma band oscillations
[c]H-response: Increased steady-state flash-VEP amplitude to frequencies of 18 Hz or above
[d]Event-related synchronization/desynchronization
[e]Post-movement beta synchronization

1.7 Conclusion

The current state of EEG in migraine is summarized in Table 1.1. A clinical EEG is not indicated in the routine evaluation of primary headaches. However, EEG should be performed during or after suspected basilar or hemiplegic migraine, in atypical headache with migraine-like features, and when headache is thought to be a symptom of epilepsy. It should also be emphasized that no imaging method, including EEG and MEG, is yet applicable for the clinical evaluation of chronic pain in individual patients [65].

Classical IPS has not revealed consistent abnormalities in migraine. However, the recently reported increased EEG reactivity in the primary visual cortex to patterned visual stimuli, using advanced EEG analysis [52], should be confirmed in blinded studies and extended across the migraine cycle.

Ambulatory long-term EEG monitoring in migraine was suggested as a useful approach previously [6]. Recently, a new smart-phone-based EEG application been developed [43], and such interesting self-application methods should be evaluated further.

EEG methods can be used to study pathophysiologic mechanisms in migraine. A slight midbrain dysfunction was proposed to explain published EEG findings in migraine [6]. Research during the last three decades has probably strengthened this notion although results and methods have varied. Subtle EEG findings in the interictal state in blinded studies may support thalamocortical instability in migraine, supporting findings from imaging studies [66] and somatosensory evoked potential studies [45, 67]. Thalamocortical instability or "dysrhythmia" is a broad concept that lacks a clear-cut definition. However, the proposed pathophysiology [68] may explain why many previously reported "EEG deviations" in migraine are like those caused by drowsiness or hyperventilation [6].

Many interesting EEG changes have been observed in the preictal and ictal states too, and it is highly recommended to perform longitudinal studies that enable paired within-subject comparisons. However, many findings are still unconfirmed. There is an urgent need for larger confirmatory and fully blinded studies [29, 69] to identify reliable and valid EEG biomarkers in migraine.

Neither the specific physiologic cause for the proposed thalamocortical instability nor its role in the cascade culminating with a migraine attack is known. However, both EEG and MEG have great potentials in future pain research, as summarized in a nice recent review [70]. More studies that aim to show how EEG rhythms are changed by sensory, sensorimotor, cognitive, and direct cortical stimulation in migraine, possibly combined with pharmacologic intervention and parallel imaging studies, are warranted.

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Chapter 2
Magnetoencephalography

Fu-Jung Hsiao, Jing Xiang, and Wei-Ta Chen

2.1 MEG: Fundamental Principles and Data Acquisition

David Cohen [1] was the first to demonstrate that weak alternating magnetic fields outside the human scalp, originating from alpha-rhythm currents, could be recorded using a magnetic detector, the so-called magnetoencephalography (MEG). Later, evoked magnetic responses were also recorded [2, 3]. MEG is a functional neuroimaging tool that identifies the dynamics of neural activation in response to external stimuli or during spontaneous resting-state activities. In combination with structural brain images and data preprocessing, the functional localizations of neural current sources derived from MEG signals can be clearly identified and mapped onto the cortical regions with source analysis (Fig. 2.1).

The main sources of the magnetic fields obtained through MEG recording are postsynaptic currents, which are generated from the pyramidal neurons because their arrangement is aligned perpendicularly to the cortical surface and activated with a certain level of synchrony. The currents from the cortical pyramidal neurons flow normally to the local cortical surface. MEG is more sensitive to synchronized neural currents tangential to the skull, particularly in the walls of cortical fissures [4]. As the cortical rhythmic activities are recorded using electroencephalography

F.-J. Hsiao
Brain Research Center, National Yang-Ming University, Taipei, Taiwan

J. Xiang
MEG Center, Department of Pediatric and Neurology, Cincinnati Children's Hospital Medical Center, The University of Cincinnati, Cincinnati, OH, USA

W.-T. Chen (✉)
Brain Research Center, National Yang-Ming University, Taipei, Taiwan

School of Medicine, National Yang-Ming University, Taipei, Taiwan

Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

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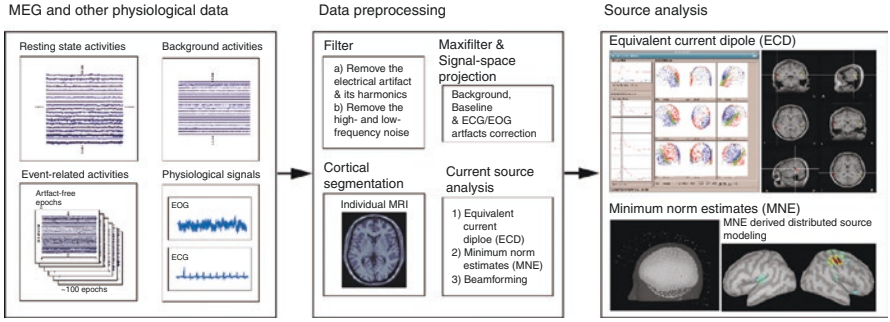

Fig. 2.1 The pipeline of MEG data processing. This example of MEG source localizations uses equivalent current dipole (ECD) and minimum-norm estimates (MNE) analysis. Note the ECD dipoles located over the bilateral auditory cortex for the auditory tone stimulation. The MNE source distributions display the primary somatosensory activation for median nerve stimulation

(EEG), the typical frequency range is 1–80 Hz in MEG. Fast ripples within the range of 500–1000 Hz are present in MEG signals and could be related to cell discharge [5] or voltage-dependent channel conductance [6]. Because magnetic fields accompany electrical currents, the density of the neural currents is proportionally transformed into the strength of magnetic fields. Therefore, by using Maxwell's equations, the magnitude of the cortical sources is derived from MEG data.

The key components with which to accomplish magnetic field recordings of the human brain are the following. (1) Superconducting quantum interference devices (SQUID): the neural magnetic fields range from approximately 10^{-14} T for evoked fields to 10^{-12} T for interictal epileptic spikes; this range is much smaller than that of Earth's field (~10^{-4} T) or urban noise (~10^{-7} T). The prerequisite for detecting the cortical evoked weak fields is a highly sensitive device with a low intrinsic noise level and high magnetic sensitivity; these characteristics are provided by superconducting loops coupled with SQUID and operated at the temperature of liquid helium (4.2 °K). (2) Shielding room: although the high-sensitivity SQUID magnetic sensor is used, the magnetic fields from Earth and environmental noise are much larger than the neuromagnetic fields—approximately 10–100 million times. For a more effective cancelation of external background disturbances, MEG recording is performed in a magnetically shielded room with alternating layers of permalloy (two layers) and aluminum (one layer).

In contrast to other functional neuroimaging techniques, such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), MEG directly measures the magnetic fields generated by neuronal ionic current instead of the secondary effects (vascular oxygen/glucose concentration) modulated by brain activities. Furthermore, MEG recording is noninvasive—it is not necessary to inject radioactive tracers as in PET scanning. Moreover, the temporal resolution in MEG is approximately 1 ms or lower, which sufficiently captures detailed neuronal dynamics and is superior to PET and fMRI. Compared

with EEG, the magnetic fields of MEG are reference free and not distorted and smeared by the complicated structure of brain tissue, skull, and bone because of the magnetic induction through the air. Thus, a markedly more precise identification of the underlying generators with source analysis techniques, such as equivalent current dipole, minimum-norm estimates, and beamforming, is obtained through MEG (spatial resolution: ~3–5 mm) compared with that obtained through EEG (spatial resolution: ~1–2 cm). Notably, MEG predominantly detects magnetic fields generated in the cerebral cortex. Subcortical activities can also be detected with a specific experimental design due to the development of new signal-analysis approaches. Therefore, noninvasive MEG recording with superior temporal and spatial resolution has been increasingly used for clinical diagnosis (e.g., presurgical ictal localization in epilepsy). MEG recording has also been used for clinical research on neurologic and psychiatric disorders [7–9].

Data acquisition is a critical part of conducting an MEG study; it has a direct effect on data quality. In the following bullets, we summarize some key points. Please refer to the article "Good Practice for Conducting and Reporting MEG Research" [10] for information on recommended practices for performing an MEG study; the study presents detailed guidelines on topics from data acquisition to data analysis.

- Preparation of the participant: Before a recording, a participant must confirm the removal of magnetic/metal materials that may distort measurements and understand the importance of avoiding head movements, eye blinks, and eye movements during trials.
- Identifying unsuitable participants: After participant is prepared for the test, he/she should be tested under a closed-eye condition for approximately 30 s, with deep breaths and opening/closing of the mouth several times to discover possible contamination of subsequent MEG data.
- Precise head position digitization: To co-register the MEG and brain MRI coordinates, using a 3D digitizer for the digitization of head shape is recommended. In addition to using head position indicators, using additional scalp points can guarantee precise MEG localization.
- Experimental design: As with the parameters of an EEG study, an MEG study also must consider the recording channels (including electro-oculography [EOG], electrocardiography, electromyography, or none), sampling rate, filter bands, number of data trials, and amplitude values of the EOG and MEG activities to reject the trial.
- Individual anatomic MRIs: Individual brain structural images are necessary for functional cortical localization, which is necessary not only for precise source localization with accurate co-registration but also for group statistics after normalization and transformation to the brain template.

In this section, we attempted to introduce some basic principles and data acquisition methods for an MEG study. Our intention was to provide some information for the migraine community to better understand the following MEG studies.

2.2 Visual Cortex Excitability in Migraine

Altered central excitability has been proposed as the potential mechanism of migraine [11, 12]. Earlier MEG studies on migraine have investigated visual cortex excitability in various migraine disorders because MEG is a technique superior to traditional scalp EEG for measuring cortical excitability. Among the various sensory modalities, the excitability change in visual cortex is of particular interest because of the clinical observations that suggest grating patterns and intense light may elicit visual illusions or migraine attacks in patients with migraine [12]. Additionally, the mechanism of migraine aura also involves spreading depression in the visual cortex [13]. As observed in most visual evoked potential studies, these MEG studies also measured habituation of the visual evoked magnetic responses to serial blocks of repetitive visual stimulation (checkerboard reversals) that lasted several minutes. Habituation refers to "a response decrement as a result of repeated stimulation," and patients with migraine often present a "lack of habituation"—no decrease or even an increase ("potentiation")—in responses following repetitive stimulation [14]. Interestingly, defective habituation appears to normalize immediately before or during a migraine attack (preictal/ictal periods) [15, 16]. Additionally, changes in habituation may be associated with the transition between episodic migraine (EM) and chronic migraine (CM). In patients with CM, the habituation pattern during interictal periods is similar to that during a migraine attack (i.e., normalized habituation), indicating CM is the status of never-ending migraine [17]. Notably, when patients with migraine were remitted from CM to EM after topiramate treatment, their habituation patterns shifted in tandem to the pattern characteristic of EM (i.e., lack of habituation) [18]. An MEG study in patients with CM and the rare phenotype of persistent visual aura documented a sustained potentiation to similar checkerboard visual stimulations [19]. To conclude, visual cortex excitability is a potential biomarker for migraine disorders, and its neuroplasticity is associated with CM evolution or remission.

The mechanisms underlying interictal deficits in habituation and the associated changes accompanying migraine chronification remain largely unknown. In general, both habituation and sensitization may result from repeated stimulation; therefore, it has been proposed that these two opposing processes compete to determine the final response [20]. Consistent with this hypothesis, an imbalance between inhibitory and excitatory cortical mechanisms—perhaps primary or secondary to abnormal thalamic control, which is in turn due to hypoactive aminergic projections from the brainstem—has been proposed as the causative factor in the abnormal habituation response.

2.3 Somatosensory Excitability and Inhibition in Migraine

Although earlier MEG studies of migraine have focused on visual habituation as mentioned earlier, those studies had limitations associated with attention control and study design. The measurement of habituation depends on patients' attention,

which can be affected by parameters of the stimuli (stimulus number, intensity, spatial and temporal frequencies, and so forth) [14, 21]. Additionally, the clinical relevance of habituation deficits has not been established in migraine or chronification for the complex neural mechanisms underlying habituation deficits, such as preactivation excitability [14, 22], cortical hyperresponsivity [21], serotonergic dysfunction [23], or mitochondria energy metabolism [24].

The "short-term" habituation, namely, sensory gating, is first introduced to measure cortical excitability and inhibition in migraine by assessing pair-pulse suppression during MEG recording [7, 25]. Sensory gating is related to habituation but is a more basic protective mechanism against sensory overload of the brain [26]. The sensory gating paradigm consists of paired electrical stimulations of 0.2-ms constant-current square waves with an interstimulus interval (ISI) of 500 ms and interpair interval fixed at 8 s [27]. The ISI of 500 ms is used because it elicits robust sensory gating phenomena [28]. The stimulus intensity is twice the subjective sensory threshold but does not elicit painful perception or visible twitches of the flexor digitorum superficialis muscle. In response to two identical stimuli during the sensory gating paradigm, the first stimulus is proposed not only to activate not only excitatory inputs that elicit the first neuronal response but also to inhibit interneuronal pathways that suppress the neuronal activity in response to the second stimulus [26]. Therefore, the peak amplitude of first responses is related to cortical excitability, whereas the amplitude ratio of the second versus first response is defined as the gating ratio, linking to the cortical inhibition.

The first MEG study using the sensory gating paradigm investigated the neuropathologic mechanism of migraine, measured primary somatosensory excitability and inhibition, and evaluated its clinical relevance in migraine [25]. This study noted the reduced primary somatosensory excitability in both CM and EM and attenuated somatosensory inhibitory capability in CM. Notably, the inhibitory function was inversely correlated with the frequency of headaches. These findings indicated that migraine is characterized by somatosensory gating deficit and the underlying excitability change reflects an altered sensory modulation, which is linked to migraine chronification. Additionally, another MEG study [7] also characterized the somatosensory gating functions in tension-type headache (TTH) and migraine and compared their excitability and inhibition measures. The somatosensory excitability was increased in TTH and decreased in migraine, with a significant group difference between both the headaches in the episodic and chronic forms. Regarding somatosensory inhibition, the capability was generally decreased in both TTH and migraine. Additionally, the excitability in TTH was positively correlated with headache frequency. The potential for using sensory gating measurement as a neuropathologic biomarker for migraine warrants further investigations.

2.4 Studies of High-Frequency Oscillations in Migraine

High-frequency brain signals are commonly referred to as high-frequency oscillations or high gamma oscillations [22, 29]. Studies have found alterations in high-frequency brain signals (>70 Hz) in migraine in the somatosensory (400–800 Hz) [22], motor (5–1000 Hz) [30–32], and other cortices [33]. High-frequency brain signals open a new window through which to objectively investigate the mechanisms underlying migraine attacks [30–32, 34].

Compelling evidence suggests that migraine is a neurologic disorder with aberrant brain activation/activity in waveforms, spectrograms, source imaging, and networks. Aberrant brain signals may be related to cortical dysexcitability or network dysfunction (Fig. 2.2) [35]. Aberrant high-frequency brain oscillations are highly correlated to clinical headache attacks [30, 36]. Cortical excitability has been conventionally assessed by measuring the amplitudes of MEG/EEG waveforms at sensor levels [37, 38]. Unfortunately, the changes of MEG waveforms at a sensor space only reflect the alteration of cortical excitability, which provides limited information about the location of the alterations of cortical excitability in the brain. Advanced MEG/EEG source imaging provides capabilities beyond the conventional visual inspection of waveforms by localizing, visualizing, and quantifying focal cortical dysexcitability [30–32]. Substantial evidence suggests that aberrant brain activities can be noninvasively detected and measured at source levels [39]. Advancements in MEG and EEG have made it possible to analyze high-frequency brain signals at source levels [40–42]. Aberrant high-frequency brain signals have been reported in migraine [31, 32, 43, 44], and normalization of high-frequency brain signals has been associated with alleviation of headache [30–32, 36]. However, it is unknown if any signatures of high-frequency brain signals are reliable biomarkers in the clinical management of migraine [31, 32, 43].

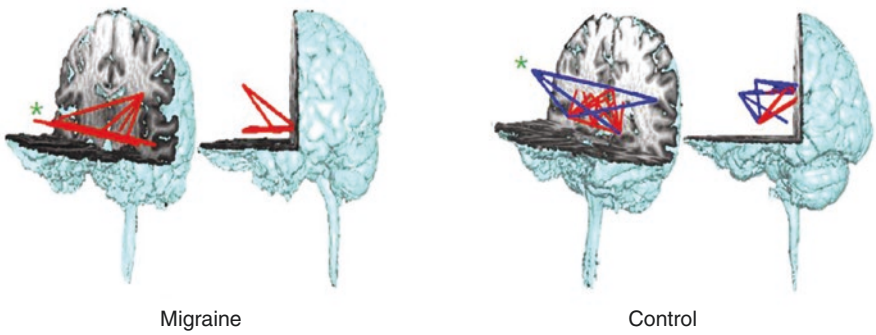

Fig. 2.2 Network of high-frequency brain signal (80–250 Hz) at source levels show significantly enhanced excitatory and diminished inhibitory connections in migraine compared to controls during a finger-tapping task (indicated by green "asterisk"). Red indicates excitatory connection; blue indicates inhibitory connection

Advanced MEG methods are considered to have a higher spatial resolution for localizing focal cortical hyper- or hypoexcitability than widely used EEG methods [45]. Newly developed methods can quantify cortical excitability with spectral and frequency signatures of neuromagnetic signals at source space [46]. An increase in spectral power represents increased cortical excitability (hyperexcitability), whereas a decrease in spectral power represents decreased cortical excitability (hypoexcitability) [38, 47]. Advanced magnetic source imaging technologies can scan the entire brain to provide spatial and volumetric descriptions of brain activities [46, 48]. A unique feature of these technologies is their ability to localize and measure the cortical excitability of the entire brain at multiple frequency ranges [46, 48], which cannot be achieved with conventional analyses of waveforms. Because normalization of cortical dysexcitability has shown promising results in migraine treatment [34, 49], localization of cortical dysexcitability can render these promising treatments even more effective [30, 36].

High-frequency brain signals are noninvasive biomarkers that can be used with conventional low-frequency brain signals (the key methodological setting is to increase the sampling rate to capture high-frequency brain signals, which will naturally include low-frequency brain signals). A substantial number of new reports on high-frequency brain signals has been noted [43, 50]. High-frequency brain signals are also crucial indicators in many other disorders (e.g., epilepsy). It is anticipated that high-frequency brain signals will be broadly adopted by the health-care community in the future.

2.5 Future Prospects

Previous MEG studies have demonstrated some potential biomarkers for migraine, such as lack of habituation and gating ratio changes. However, further studies are needed to validate these findings. Previous reports on electromagnetic stimulation have shown that normalization of cortical excitability can alleviate migraine headache [51] but requires that the stimulation location of the brain be subjectively selected. With more precise information about an individual patient's cortical excitability—where and to what degree the excitability is occurring in the brain [51–53]—the effectiveness of the aforementioned methods, such as transcranial magnetic stimulation (TMS), could be significantly enhanced. The studies of high-frequency brain signals can not only address these weaknesses but also provide new diagnostic and prognostic biomarkers and assist in the development of unprecedented therapeutic solutions for migraine. Many MEG/EEG methods, including artificial intelligence (AI), have been developed for detecting high-frequency brain signals [40] and have shown their capability to extract critical information from high-dimensional and heterogeneous data to predict and classify clinical conditions [54]. Evidence suggests that migraine attacks can be predicted and classified [55]. Because some methods have been validated with invasive recordings ("gold standard") and powered with AI, it is anticipated that newly developed methods can meet the challenges

in headache research. Finally, the simultaneous recording of MEG and EEG may also have a broad clinical effect. MEG provides unprecedented spatial resolution and EEG provides wide accessibility for migraine studies [56]. Research suggests that the complementary information obtained from MEG and EEG data can be used to identify the most specific and sensitive biomarkers for migraine. Source imaging of high-frequency brain signals, which are computed with new MEG/EEG methods powered with AI, are considered entirely new frontiers in migraine research.

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Chapter 3
Evoked Potentials

Gianluca Coppola and Delphine Magis

Abbreviations

ACE	Angiotensin-converting enzyme
BAEP	Brainstem auditory evoked potentials
CM	Chronic migraine
CSP	Cortical silent period
ICHD	International classification of headache disorders
IDAP	Intensity dependence auditory evoked cortical potentials
MEG	Magnetoencephalographic
MEP	Motor evoked potential (MEP)
MOH	Medication overuse headache
NSAIDs	Non-steroidal anti-inflammatory drugs
PT	Phosphene threshold
rTMS	Repetitive transcranial magnetic stimulation
SS	Steady-state
SSEPs	Somatosensory evoked potentials
sTMS	Single-pulse transcranial magnetic stimulation
TMS	Transcranial magnetic stimulation
VAS	Visual analogue scale
VEP	Visual evoked potential

G. Coppola (✉)
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy
e-mail: gianluca.coppola@uniroma1.it

D. Magis
Neurology Department & Multimodal Headache and Pain Management Clinic, CHR Verviers East Belgium, Verviers, Belgium
e-mail: delphine.magis@chrverviers.be

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3.1 Introduction

Headache is a widespread symptom that frequently leads patients to consult a neurologist. Most recurrent headaches will occur in the context of a primary headache disorder, which can be classified based on the criteria of the new ICHD 3 classification (2018). Few chronic headaches are directly related to an identifiable underlying organic condition (secondary headaches). Even if the diagnosis of a primary headache is predominantly a matter of clinically based reasoning, the quest for a specific biomarker of various primary headaches (predominantly migraine) has been among the biggest challenges of the last 50 years.

Numerous paraclinical tests have been developed over the past decades and used to gather a better insight into primary migraines' pathophysiology, but their usefulness and place in clinical practice are sometimes ill defined. Functional neuroimaging techniques, such as positron emission tomography and functional magnetic resonance imaging, offer a high spatial resolution, while electrophysiological techniques have an excellent temporal resolution and probably a better accessibility in daily neurological practice. Laboratory testing provided promising results but is usually restricted to tertiary headache centres.

Electrophysiology is particularly suitable to study the nervous system in human beings. It is noninvasive, riskless and relatively easy to perform. Briefly, the different components of the nervous system generate an electrical signal that reflects the summation of several action potentials and can be recorded using surface scalp electrodes. Transient evoked potentials are electrical potentials elicited in the nervous system after repeated stimulations (visual, auditory, somatosensory, etc.). Transcranial magnetic stimulation (TMS) allows evaluating temporal changes in cortical excitability.

Here, we will review the relevant data of electrophysiology using non-cognitive and non-painful evoked potentials performed in migraine and their interest for the phenotyping and diagnosis of long-lasting headache disorders.

3.2 Visual Evoked Potentials

Migraine is associated with prominent visual symptoms; it thus seemed logical to initially study the visual modality of evoked potentials. The latter is still the most studied evoked modality.

For more than six decades, the recording of visual evoked potentials (VEPs) has been used in neurophthalmological diagnostics as a complement to ophthalmological and neurological semiotics.

The recording of VEPs is a method that has the great advantage of exploring, in a noninvasive way, the functioning of the visual system. The VEP, in fact, represents

the summation of electrical potentials recorded over the scalp, which mirrors the neurophysiological counterpart of the activity of the visual pathway up to Brodmann area 17.

Different types of visual stimulation paradigms have been used to study migraine pathophysiology.

The bioelectric activity of the innermost retinal layers (cells and ganglion fibres), explored through pattern electroretinogram recording, showed no abnormalities in migraine with and without aura [1, 2].

By using a repetition of the visual stimulus above 4 Hz, it is possible to obtain a stationary neurophysiological response over time, so-called steady-state (SS) response, that can be analysed using a Fourier transform, that is without the intervention of the examiner. A higher amplitude of the fundamental harmonic from SS stimulation is commonly found in episodic migraine with or without aura [3–7]. This abnormality returns to the normal range after a prophylactic treatment with femoxetine or propranolol [8]. In a multichannel study the connectivity between the SS-VEP response recorded from the cuneus and that recorded from the temporal poles and the anterior cingulate cortex increased with increased headache-free days elapsed since the last migraine attack [9]. Some researchers found that relative reduction in SS-VEP response with increasing contrast—an indirect measure of contrast gain—is more common in migraineurs, consistent with increase in feedback excitation driving increased inhibition and leading to increased perceptual surround suppression [10].

Studies that analysed the amplitude of flash or pattern evoked potentials were inconclusive as they found either an increase [11–21], a decrease [17, 22, 23], or a response similar to that in healthy subjects [11, 24–31]. However, since the gross portion of the neural activity is lost after the standard process of averaging an amount of traces, Lisicki et al. investigated VEPs using single-trial analysis, detecting greater VEP amplitudes in episodic migraine-without-aura patients than in healthy volunteers. Moreover, they observed that higher single-trial VEP amplitudes in migraine involve higher grey matter volume and peculiar pattern of functional connectivity in brain areas devoted to visual processing [32].

Another common finding in migraine is an increased asymmetry between the electrophysiological responses of the two hemispheres [1, 23, 33–39].

In recent years, most of the scientific literature on neurophysiology of migraine has focused on the study of habituation mechanisms. 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. 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 fact, by acquiring a high number of trials and averaging them off-line into successive blocks, it is possible to study the course of the amplitude of the potential over time. In healthy subjects, the amplitude of evoked potentials shows a reducing response during stimulus repetition, that is habituates normally [40].

The majority of studies performed interictally in groups of episodic patients have shown a lack of reducing response, that is a habituation deficit, between the first and the following blocks of pattern-reversal VEPs [13, 26, 28, 41–61] (Fig. 3.1).

Habituation deficit was also found for visual evoked magnetoencephalographic (MEG) responses [62–65] and motion-onset VEPs evoked by the abrupt onset of visual motion, which are generated in extrastriate areas [53].

The habituation deficit of the visual system seems to have a genetic basis as it is also present in the unaffected relatives of migraine patients, defined at-risk [44, 66]. In addition, this abnormal processing of visual information changes in relation to where you are during the migraine cycle, being maximum as the distance from the last attack increases [20, 58] and minimum, normalizing, during an attack [49, 58, 62] and after pharmacological [45, 50] and non-pharmacological [42, 43, 51, 52, 67, 68] treatment. It might depend on sunlight irradiance [47] and the patient's self-perceived stress [46]. Sunlight and genetics, among others, could perhaps account for some discrepancies between VEP studies, since not all of them retrieved a habituation deficit in the interictal phase [31, 41]. An anomalous thalamic control of the flow of information reaching the cortex [54], which in turn causes an altered degree of lateral inhibition of the visual cortex [58], studied by means of a windmill/dartboard pattern, seems to be at the basis of this functional anomaly. The mechanisms of cortical inhibition have also proved to be altered when the VEP technique of double visual stimulation was used in both migraine without [69] and with aura [70]. It is possible to intervene on the habituation curve in general and on its deficit in migraine during the interictal phase through various experimental methods, such as tonic pain [71], 3 min of forced hyperventilation [55], or 2 h of light deprivation [57]. The huge number of factors influencing the phenomenon of habituation may explain why some studies did not confirm this abnormal processing of visual information between migraine attacks [19, 31, 72–78]. We do not know whether these contradictory results are due to the enormous number of factors that can influence the final response after repeated visual stimulation or due to the lack of a diagnosis and blind analysis of the recordings, as others think [75]. Anyhow, lack of VEP

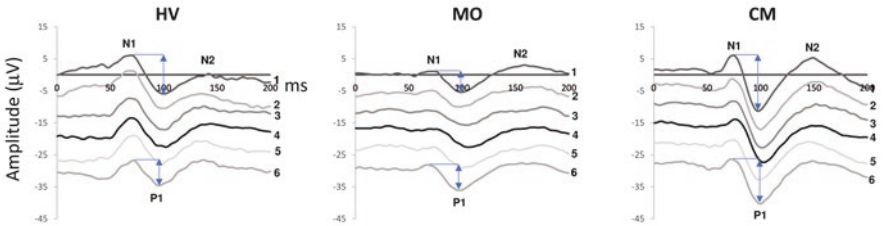

Fig. 3.1 Demonstrative recordings of pattern-reversal visual evoked potentials (VEPs) in a healthy volunteer (HV), a migraine–without-aura patient between attacks (MO) and a chronic migraine patient (CM). VEPs are six consecutive blocks of 100 averaged responses during uninterrupted stimulation. Compared to the healthy subject, the MO patient is characterized by a tendency to be lower N1-P1 amplitude of the first block of averaged responses and lack of habituation over successive blocks of responses, while the CM patient is characterized by an higher amplitude of the first block of averaged responses and normal habituation over successive blocks of responses

amplitude habituation was detected even in patients affected by the recently described neurological condition called ‘visual snow’ syndrome [79–81], which may share pathophysiological mechanisms with migraine [82].

3.3 Somatosensory Evoked Potentials (SSEPs)

The recording of SSEPs is an objective and quantifiable measurement of the functioning of the lemniscal somatosensory system. The amplitude and latency of standard grand-averaged cortical median nerve SSEP response were normal in episodic migraine between attacks in most of the studies [59, 83–90], although increases in amplitude were reported in the only study that used magnetoencephalography [91]. The amplitude of the N20 SSEP component was delayed and reduced during a sensory aura in one patient, and both anomalies progressively returned within the range of normality during the subsequent headache phase [92].

As for the VEP amplitude, a lack of habituation to repetitive peripheral electrical stimulation has been observed to the SSEP amplitude (Fig. 3.2). This altered processing of sensory information was observed during the pain-free phase [59, 86, 93–97], normalizing immediately after a forced increase in cortical excitability [94, 97] and after a dietary ketogenic regimen [42], but not after anodal transcranial direct current stimulation of the temporal pole [43]. An abnormal thalamic control, through thalamic radiation, of the degree of cortical activation could explain the habituation deficit [94, 95]. Nonetheless, the magnitude habituation deficit is significantly correlated to the clinical evolution of migraine, since spontaneous worsening of the disease is associated with further reduced habituation, whereas spontaneous improvement is linked with enhanced habituation [96].

In partial agreement with the VEP results, during a migraine episode, initial response increased has been observed to the SSEP amplitude, while delayed

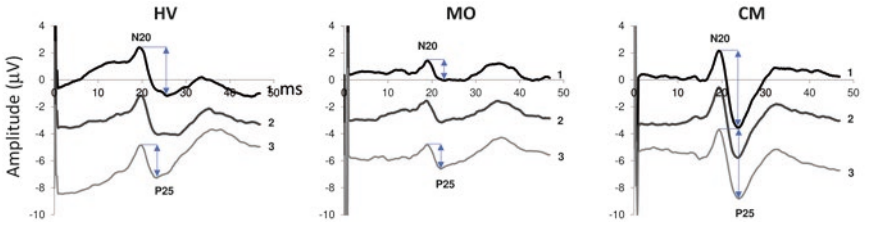

Fig. 3.2 Demonstrative recordings of median nerve somatosensory evoked potentials (SSEPs) in a healthy volunteer (HV), a migraine-without-aura patient between attacks (MO) and a chronic migraine patient (CM). SSEPs are three consecutive blocks of 100 averaged responses during uninterrupted stimulation. Compared to the healthy subject, the migraineur is characterized by a lower N20-P25 amplitude of the first block of averaged responses and lack of habituation over successive blocks of responses, while the CM patient is characterized by an higher amplitude of the first block of averaged responses and normal habituation over successive blocks of responses

responses showed normal habituation [93, 95]. This response pattern has been interpreted as a possible neurophysiological expression of a transient central sensitization process during an attack. As with VEPs, a reduced degree of lateral inhibition within the somatosensory cortex could help explain this habituation deficit, closely related to the degree of thalamocortical activation. In pain-free patients, the percentage of lateral inhibition correlated negatively with the days elapsed since the last migraine attack, the average duration of the attacks and the severity of the headache, measured on a VAS scale [98]. It is of interest that in migraine, a reduced inhibition of SSEP amplitude during both a sensory gating [99] or recovery cycle paradigm [88] after paired electrical stimuli was observed, which may be yet other findings in favour of a less-efficient subcortical inhibition of sensory cortices [100]. In fact, in adult migraineurs, shortened recovery cycle correlated with reduced thalamocortical activation as well as with clinical worsening [101]. Migraine prevention with topiramate normalized the abnormal recovery cycle [102].

Again, as with VEPs, a significant asymmetry between the two hemispheres was noted even when recording the N30 SSEP amplitudes [85]. In an old study comparing patients with mixed headache (migraine and tension-type headache) and pain-free controls, parietal cortical potential was found to increase in amplitude and more rapidly as the stimulus intensity increased, independent from having or not having headache during the testing session [103].

3.4 Auditory Evoked Potentials

After an acoustic stimulus, up to 30 waves can be recorded at cortical level: from the far-field ones generated at cochlear and acoustic nerve levels to those generated in the auditory cortex and associative acoustic centres. These responses are generally categorized into early, middle and late potentials. In most studies researchers were not able to find interictal abnormalities in the baseline parameters of early short-latency brainstem auditory evoked potentials (BAEP) [31, 33, 104–107], with the exception of a prolonged peak latency of wave V during [107] and between [108] attacks.

Some authors found significant I–III [109], III–V [25, 109], or I–V [25, 108, 109] BAEPs interpeak latency differences when comparing patients with controls and, in some case, even comparing patients recorded between attacks with those during attacks [107, 109]. In another study, all BAEP latencies increased and the V/I peak amplitude ratio decreased during the attacks [110].

Also with this neurophysiological method an interhemispheric asymmetry of the responses, specifically that of the interpeak latency I–V, has been detected [104, 106]. BAEP abnormalities did not change after flunarizine [104].

Deficient habituation mechanism of waves IV–V dispersion was found in migraine interictally in response to 40 dB clicks (but not to 55 and 70 dB clicks) in a blinded study, in which a direct relationship between BAEP amplitudes and blood 5-HT levels was also reported in controls but not in migraineurs [111].

Two studies [112, 113] but one [31] found stronger stimulus intensity dependence of late, long-latency, auditory evoked cortical potentials (IDAP) between attacks in migraineurs compared with healthy controls. Coherently with other neurophysiological data, IDAP normalizes during an attack [49]. Lack of habituation has also been reported for cortical auditory evoked responses for 70 dB [112], but not in another one [31]. An inverse correlation between amplitude habituation and IDAP has been reported [113] (Fig. 3.3). In a recent study, researchers assessed auditory middle-latency evoked potentials in a group of patients with vestibular migraine. They described a lack of habituation of Na-Pa amplitude to repetitive stimulation when compared with patients affected by Meniere's disease and healthy subjects [114].

In an auditory P50 event-related potential paradigm, auditory sensory gating was markedly decreased in migraine patients compared with controls [115, 116], probably in a way that is related to reduced short-term habituation.

3.5 Single-Pulse Transcranial Magnetic Stimulation (sTMS)

Noninvasive magnetic stimulation of the brain is a well-established neurophysiological method to assess the excitability of the underlying cortical area. After the introduction of TMS in 1985 [117], several authors have used sTMS in migraine studies.

In migraine, both decreased [118, 119] and increased [120] phosphene threshold (PT) were reported when sTMS was applied over the visual cortex. Several studies also found no differences compared to controls [77, 121]. A systematic review of the studies using sTMS to assess visual phosphenes provided evidence for higher

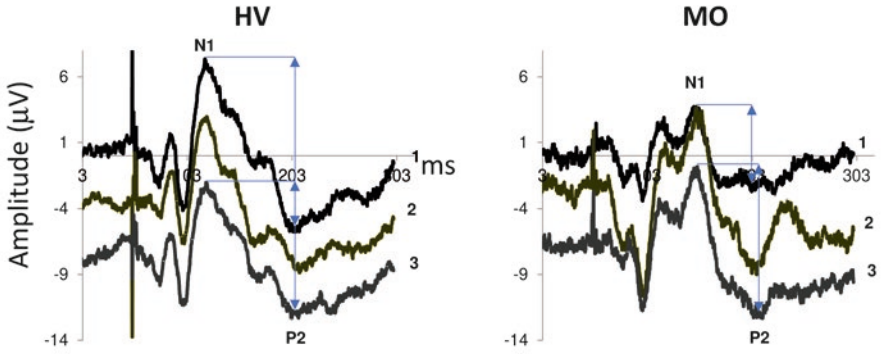

Fig. 3.3 Demonstrative recordings of intensity-dependent auditory evoked potentials (IDAP) in a healthy volunteer (HV) and a migraine-without-aura patient between attacks (MO). IDAPs are three consecutive blocks of 50 averaged responses during uninterrupted stimulation (80 dB). Compared to the healthy subject, the migraineur is characterized by lack of N1-P2 amplitude habituation over successive blocks of responses

phosphene prevalence and lower threshold in migraine with aura patients compared with controls, but not in migraine-without-aura patients. They concluded that these results should be interpreted with caution [122]. In migraine, PT did not correlate with VEP amplitude and habituation [60] or with average pain intensity, disability assessment scales, gender, age, migraine subtype, migraine duration and use of hormone contraceptives [123]. Unfortunately, the assessment of PT has a clear shortcoming as it relies only on the subjective patient's experience (describing positive visual phenomena or not). This concern is not retrieved in motor cortex TMS, where the threshold is assessed through an objective and recordable measure, the amplitude of motor evoked potential (MEP) recorded from a peripheral muscle. Like PTs, thresholds for MEPs were found to variate widely, being normal [51, 118, 124–127], increased [128–130], or reduced [131–133] in migraineurs. 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 [134]. However, some authors showed that these inconsistent findings resulted from variation in the cortical excitability related to the time interval between the ictal and interictal states of migraine [135].

Using paired-pulse TMS, intracortical facilitation was found in one study [136], but not in another [130]. The cortical silent period was normal [118, 136] or reduced [137, 138] in migraine patients between attacks. In migraine with aura patients, the conditioning of the cerebellum with TMS showed a significant deficit of cerebellar inhibition on the motor cortex compared with controls [139].

3.6 Evoked Potentials in Chronic Migraine (CM)

The mechanisms by which an episodic form of migraine becomes chronic are still unknown. Neurophysiology has also tried to help solve this issue.

One of the mechanisms supposed to be the basis of this process is central sensitization. According to its definition, that is increased responsiveness not only to noxious but also to innocuous peripheral stimuli, neurophysiological signs of sensitization have been reported recording SSEPs. Amplitudes of the parietal components were larger in patients experiencing CM or medication overuse headache (MOH) than in episodic migraine patients between attacks [93, 95, 140].

By the investigation of simultaneous SSEP habituation and thalamocortical loop activation in CM, researchers have observed a neurophysiological pattern similar to that of ictal episodic migraine. In fact, both episodic and chronic patients were characterized by higher initial amplitudes, reflecting cortical sensitization, and by response habituation over sequential block averages, resulting in a 'transient' cortical sensitization. In MOH, the initially higher SSEP amplitudes lacked habituation in subsequent block averages, that is further increase, resulting in a 'persistent' cortical sensitization [93]. Lack of SSEP amplitude habituation in MOH patients

differed according to the overused drug, because amplitudes were smaller in triptan overusers than in patients overusing non-steroidal anti-inflammatory drugs (NSAIDs) or combined medications [93]. Interestingly, patients experiencing cutaneous allodynia exhibited greater SSEP amplitudes compared to those without allodynia, confirming this abnormal cortical response in the neurophysiological counterpart of central sensitization [59]. Moreover, the neurophysiological abnormalities of MOH are proportional to the duration of the chronic phase [93, 140]. These abnormalities in cortical responses to somatosensory stimulation appear to be strongly influenced by genetic factors [141]. That angiotensin-converting enzyme (ACE) polymorphism could affect neural plasticity was assessed by SSEP recording and the clinical features of MOH patients. The D/D ACE homozygote carriers exhibited the highest grand-averaged SSEP amplitudes (i.e. reflecting sensitization) and the most severe deficits in habituation, although other MOH patients overall did not habituate either. This abnormal neurophysiological pattern gradually disappeared in the D/I and I/I carriers, in whom the cortical response habituated normally [141].

In a recent study, we found that, contrary to the episodic migraine, the level of somatosensory cortex lateral inhibition is normal in CM patients without a previous history of medication overuse. Moreover, in contrast with the idea that deficient cortical inhibitory mechanism plays a pivotal role in the basic mechanisms of central sensitization in CM, we did not find a clear correlation between the degree of lateral inhibition and of sensitization [140]. Nonetheless, less-efficient subcortical inhibition of sensory cortices cannot be excluded, since in an MEG study of somatosensory gating, reduced parietal responses to paired-pulse stimuli were more pronounced in CM than in episodic migraineurs and healthy controls [99].

Compared with episodic migraine patients recorded interictally, CM patients showed greater initial mean block amplitude in recordings of magnetic VEPs [63]. Moreover, consistently with the above-mentioned SSEP studies [93, 95], VEP amplitudes habituate normally during stimulus repetition in CM [63, 142] and may change with the transition from CM to episodic migraine after topiramate treatment, switching from normal to deficient habituation [65].

A group of CM patients, most of them with MOH, had a steeper IDAP than healthy controls, which significantly flattened after greater occipital nerve block significantly reduced monthly days with headache [142].

By further exploring inhibitory circuits, Currà et al. [138] measured the transcranial magnetic stimulation (TMS)–induced cortical silent period (CSP) in a group of MOH patients. Despite the overall similarity in SP duration between MOH patients and healthy controls, subgroup analysis revealed that CSP duration was significantly shorter in triptan overusers than in the NSAID or triptan-plus-NSAID overuser groups. In MOH patients overall, CSP duration correlated positively with monthly tablet intake. However, this positive correlation was restricted to NSAID and triptan-plus-NSAID MOH subgroups; triptan overusers exhibited a negative correlation [138].

3.7 Conclusions

Studies of evoked potentials in migraine show that the migraine brain processes sensory information differently from the brain of healthy subjects. In fact, the most frequently detected peculiarity during the migraine pain-free phase is an excessive cortical responsiveness to any type of sensory stimulation (except olfactory stimulation). This over-responsiveness manifests either as an increased amplitude of the grand-average potential or as a deficit of habituation during a series of stereotyped stimulation. Besides this habituation deficit, migraineurs exhibit an increased intensity dependence of auditory evoked potentials, which was found to be correlated to the lack of habituation and perhaps to be its consequence. Habituation is a phenomenon intrinsically linked to learning and memory. Precisely as a function of the latter phenomenon, the brain can undergo a series of plastic modifications, which have been shown to be altered in migraine, when studied, for example, with repetitive TMS [143].

The cortical hyper-responsiveness is not constant in migraine patients and may not be reproducible. The reasons for these between-studies discrepancies are multifaceted, and they reflect the complex pathophysiology of the disease:

- First, it was shown that the degree of habituation depended on technical parameters, for example the temporal or spatial frequencies of a visual pattern, or the blinding of the researchers performing the analysis, even if a recent publication actually found no difference between blinded and non-blinded habituation assessments of a same population [144]. Nonetheless, previous studies conducted in the same laboratory have shown that whether blinding the analysis [20, 53, 144] or attempting to blind the diagnosis [31, 75], the result remains unchanged.
- Second, habituation is a dynamic parameter that provides interesting data about the current ('cross-sectional') CNS information processing. Sequential recordings have demonstrated that the cortical dysfunction level varied with the migraine cycle, being prominent with the increasing distance from the last attack and absent during an attack. In CM, the neurophysiological pattern is quite similar to that derived from recordings from patients with episodic migraines derived during an attack [95, 98] and was previously defined as a condition of 'never-ending migraine attack' [145].
- Third, genetics appears to be a determinant factor of the interictal dysfunction leading to deficient habituation in migraine. Hence, habituation deficit could thus be an endophenotypic marker of a genetic predisposition to migraine, even if these conclusions cannot be applied to individuals.
- Fourth, the habituation can be modulated by external interventions, especially drugs known to alleviate migraine attacks, as well as non-pharmacological intervening procedures.

Therefore, the sole habituation deficit cannot be considered as a formal diagnostic criterion of migraine, but could help in the case of atypical presentations.

However, a multicentre study performed in 624 patients recently demonstrated that combining the recordings of visual (habituation) and auditory (intensity dependence) evoked potentials could characterize interictal episodic migraineurs with 83.4% sensitivity, 66.7% specificity and 81.1% accuracy [146].

Only now are we beginning to see the possibility that these functional abnormalities are extrinsic in morphofunctional abnormalities of the brain [147]. Further studies are needed to better understand the clinical correlates of this altered information processing in the migraine brain, also with the ultimate aim of intervening in a more targeted way both pharmacologically and non-pharmacologically.

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Chapter 4
Cognitive Potentials

Marla J. S. Mickleborough, Gloria Sun, Daneil Moss, and Conley Kriegler

For a migraine sufferer, what it is to be a migraineur goes beyond the actual headache experience. A migraineur may feel that he/she is impacted in daily activities, even when not suffering from a headache attack. Of course, it has long been reported that migraineurs feel sensitive to lights, sounds, smells, and distractions in day-to-day life [1]. In fact, empirical evidence has led to migraine being considered to be a form of sensory processing disturbance [2], with substantial evidence implicating hyperexcitability of sensory cortices in migraine between attacks [3–6]. More recent research has indicated that this is not just a sensory experience as more cognitive levels of performance are affected in migraine, especially attentional processing. Anecdotally, migraineurs themselves often agree with these findings, suggesting that they have difficulty ignoring background stimuli and feel exhausted after a busy outing. This chapter explores the research using ERPs (event-related potentials) from EEG (electroencephalogram) recordings to study cognitive differences between migraineurs and non-migraine control participants.

4.1 Sensory Habituation

To begin with, decreased sensory habituation (measured via EEG recordings) has been one of the most widely accepted findings in migraine and has been considered by some to be a neurophysiological hallmark of migraine [6–8]. Specifically,

M. J. S. Mickleborough (✉) · G. Sun · D. Moss
Department of Psychology, University of Saskatchewan, Saskatoon, SK, Canada
e-mail: marla.mick@usask.ca

C. Kriegler
Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

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when migraineurs watch visually repetitive stimuli, such as a repeated flash or checkerboard reversal, they do not show the normal pattern of habituated visual sensory responses [5, 7, 9–16]. Normal populations reveal a gradual and automatic attenuation in the strength of sensory-evoked cortical responses to repeated visual stimuli; instead, migraineurs have either no change or even an increase in amplitude [5, 7, 9–16].

Importantly, sensory habituation is proposed to protect the cortex against sensory overload [5, 17, 18] via a gradual decrease in the brain response to repeated non-harmful, non-beneficial repetition of a visual stimulus [17–19]. It is this protective mechanism of habituation that is found to be lacking in migraineurs [20]. Given that human attentional processing can be influenced by sensory experience, we might expect this hypersensitivity to normal sensory inputs to have a forward cascade of effects on cognitive processing in migraineurs and in attentional networks in particular.

4.2 Visual Spatial Attention

Early research assessing attentional processes in migraineurs often used indirect measures of visual attentional processing and were both contradictory and inconclusive. For example, there were a number of investigations of migraineur attention relying on visual search tasks, where participants look for a visual target embedded within an array of distracting elements. While one study of visual search found faster search time in migraineurs [21], others reported no differences between migraineurs and controls [22–24]. Other attempts were made to assess attentional functioning in migraine using paper-and-pencil or clinician-administered neuropsychological test batteries where participants were given a series of psychological tests (such as the Weschler Adult Intelligence Scale [WAIS]), and attention was just one of the many components being indirectly assessed (for example, via subtests of the WAIS in which attention is required to repeat numbers and letters in reverse or in a chronological order). Again, results from these studies are contradictory, with some finding attentional deficits [25], while others finding no attentional abnormalities in migraineurs [26].

While these early studies painted a picture that migraine did not affect cognition in between headache attacks, more recent EEG research of cognitive potentials presents a view that migraineurs have anomalies specifically pointing to increased allocation of attention to extraneous environmental stimuli. Described across studies reviewed below, it is revealed that, between attacks, migraineurs manifest heightened sensory responses for to-be-ignored visual stimuli, increased bottom–up attentional orienting (visual and auditory), and overall increased evaluative processing of visual stimuli.

4.3 Cognitive Potentials

4.3.1 Abnormal Top–Down Attention

Given that top–down attentional control signals can affect excitability of sensory response in visual cortex, it makes sense that normal attentional modulation is affected in migraineurs. Namely, research supports that when a migraineur consciously orients their attention to a discrete location in visual space (top–down attentional control), they nevertheless manifest heightened cortical responses to events outside their zone of attentional focus, as measured via ERPs [27]. It is important to note here that the normal response to such stimuli is that the strength of sensory-evoked cortical activity engendered by a stimulus directly varies with the amount of attention someone is paying to the location of that stimulus and involves an active suppression of activity for unattended stimuli. In contrast, when migraineurs were presented a probabilistic spatial orienting task while ERPs of attended versus unattended foveal and parafoveal stimuli were recorded, the results revealed that, relative to controls, migraineurs lacked the normal increased cortical activity to *attended* parafoveal events (as measured via the early P1 ERP), while the N1 ERP component actually revealed an increased cortical response to *unattended* events at the fovea [27] (see Fig. 4.1).

4.3.2 Increased Bottom–Up Attentional Orienting (Visual and Auditory)

In light of this finding of increased sensory responses for to-be-ignored visual stimuli, one would expect sudden-onset stimuli in a migraineur's visual periphery might manifest heightened bottom–up attentional responses. A non-predictive visual spatial cueing task that relied on stimulus-evoked responses in visual cortex for triggering attentional orienting revealed that migraineurs have increased bottom–up attentional orienting to sudden-onset stimuli in unattended visual space as compared to controls [28].

In auditory attention research, Morlet et al. studied automatic attentional orienting via migraineurs' EEG response to a passive auditory oddball task [29]. They found an enhanced N1 ERP orienting component, which shows that migraineurs have an increased automatic attentional orienting to auditory stimuli, especially for auditory changes but also more generally to any incoming auditory stimulus [29]. Similarly, Demarquay et al., using a classic auditory habituation paradigm, reported evidence of an increased N1 orienting component toward auditory stimuli in migraineurs compared to healthy controls [30]. However, to the authors' surprise, migraineurs' pattern of short-term and

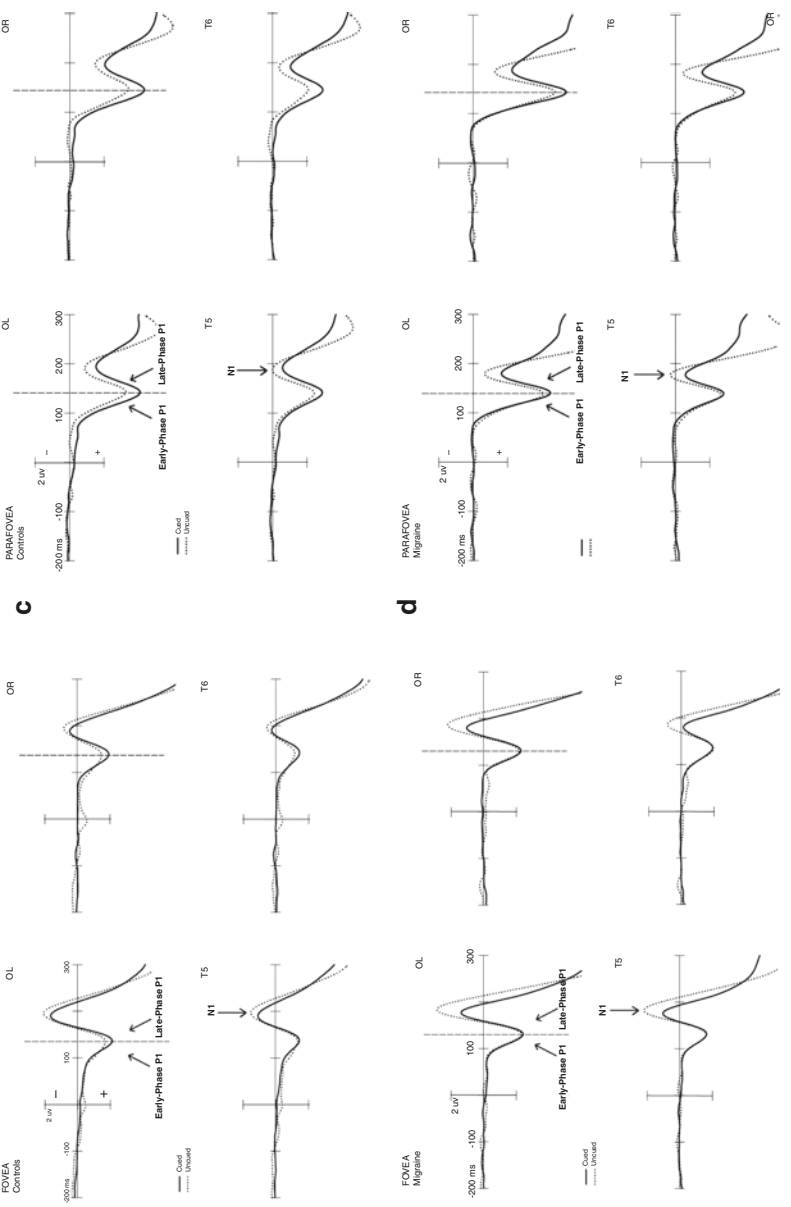

Fig. 4.1 P1 and N1 component responses to targets. All waveforms are displayed relative to a baseline of −200 to 0 ms prestimulus. Shown are the waveforms from lateral posterior electrode sites for foveal targets in (**a**) control group and (**b**) migraine group and parafoveal targets in (**c**) control group and (**d**) migraine group (Modified from Neuropsychologia, 49: 1006–1015, with permission from Elsevier")

long-term habituation was the same as that of controls. They conclude this indicates migraineurs have enhanced automatic attentional orienting toward sound stimuli [30].

4.3.3 P3 Components (Visual and Auditory)

Given the attentional abnormalities described above, and especially the lack of attenuation of behaviorally irrelevant stimuli, we might consider whether cortical hyperexcitability extends into more cognitive components, where processing of behaviorally relevant stimuli may be impacted by attentional control. For example, during mind wandering there is normally a general attenuation of processing of external stimulus inputs. Given that controls show an attenuation response in mind wandering to unattended visual stimuli and previous work shows migraineurs have a lack of attenuation of unattended visual inputs [27], Kam et al. sought to determine whether migraineurs might lack normal attenuation during mind wandering. While recording ERPs, participants performed a visual sustained attention to response task (SART), during which they were occasionally prompted to report their attentional state as either on task or mind wandering. Results showed that, similar to controls, migraineurs *do* manifest an attenuation in the neurocognitive response to task-relevant visual events as they mind wander as measured via P3 ERP component [31].

Guo et al. evaluated the spatial attention functionality in migraineurs using a visual oddball paradigm while collecting ERP data [32]. They reported P300 amplitudes were reduced in migraineurs, and the cognitive abnormalities associated with such a reduction in ERP amplitudes directly correlated with the onset of migraines, both in prevalence and in length [32]. Similarly, other research reveals that cognitive dysfunction in migraine can be related to the duration and the frequency of headache [33]. Specifically, Huang et al. administered several cognitive and psychological tests and recorded EEG P3 latency during a target recognition task (e.g., respond to displayed number 2, ignore displayed number 8). ERP results showed P3 amplitudes were equal, while P3 latency was prolonged in migraineurs as compared to controls. Migraineurs showed deficits in cognitive functioning on common neuropsychological tests, and poorer performance was specifically associated with frequency and duration of migraine attacks.

In auditory research, Titlic et al. attempted to characterize the P300 component of ERP data in migraineurs utilizing an auditory oddball paradigm [34]. The migraineurs demonstrated an increased P300 latency in response to both target and frequent auditory stimuli, which is indicative of cognitive processing abnormalities not observed in control participants. These cognitive impairments suggest delayed processing of auditory stimuli in migraineurs [34]. Another study by Chen et al. used a passive oddball test with EEG recordings to detect passive auditory attention. They reported no differences in latencies of N1, P2, N2, or P3, but reported decreased P3 amplitude of the

passive paradigm single-tone elicited ERPs in patients suffering from migraine, which might indicate a deficit of passive auditory attention in migraineurs [35].

4.3.4 Emotionally Valenced Cognitive Potentials

Given the attentional abnormalities in migraineurs reviewed above and that emotional stress can trigger migraines, it is possible that migraineurs show abnormal ERP response to emotional stimuli. In fact, Andreatta et al. found migraineurs had altered cortical activity linked to the processing of emotional information—specifically with larger amplitudes to angry faces [36]. In their study, migraineurs and controls were first given a passive viewing task of angry, happy, and neutral facial expressions. Following the initial viewing, participants viewed the facial expressions again and were prompted to rate valence and arousal of the images. Results showed that although the valence and arousal ratings were the same for migraineurs and controls, the N170 amplitude elicited by angry facial expressions as compared to neutral facial expressions was significantly larger in migraineurs than in controls. Andreatta et al. concluded that angry facial expressions are "quickly and strongly processed" by the migraine group and that migraineurs have enhanced early processing for highly arousing and threatening social stimuli as compared to controls.

However, Steppacher, Schindler, and Kissler had migraine patients and controls watch positive, negative, and neutral pictures from the International Affective Picture System (IAPS) while EEG recordings were taken [37]. They concluded that migraineurs have increased cortical response to all the presented pictorial stimuli, regardless of emotional content [37]. While migraineurs and controls did not differ in valence or arousal ratings, migraineurs had enhanced cortical ERPs during both early and late stages and specifically had larger late positive potential (LPP). It appears that migraineurs seem to allocate more perceptual and cognitive resources to all kinds of stimuli than controls do.

Our research supports this increased perceptual and cognitive reaction to images and reveals that the response increases across time [28, 38]. While migraineurs showed heightened evaluative processing over time consistent with an increase in motivational attention toward everyday logos, this coincided with decreased implicit evaluative categorization of visual stimuli [28, 38]. Participants viewed a set of unfamiliar commercial logos, which then repeated ten times (ten blocks) in the context of a target identification task while brain responses were recorded via ERPs. Following this task, participants individually identified those logos that they most liked or disliked. Two key results suggested migraineurs have abnormal implicit evaluative processing of visual stimuli. First, our data suggested migraineurs had an increasing level of cognitive analysis over time, increasing in amplitude across the ten blocks (see Fig. 4.2). Second, migraineurs lacked a bias for disliked logos. Taken together, these results suggest that migraineurs are not only evaluating attended environmental stimuli more than controls over time, but also not adequately hedonically categorizing it for quick allocation of attention.

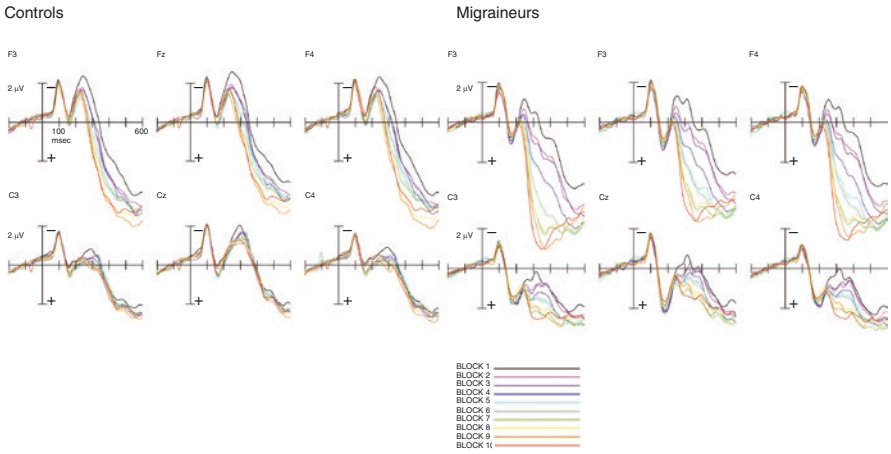

Fig. 4.2 Grand-averaged ERP waveforms as a function of group, block, and scalp location. Control group ($N = 25$). Migraine group ($N = 25$). Shown are frontal-central electrodes F3, FZ, F4, C3, CZ, C4 with first block (black line) through to tenth block (red line). doi: https://doi.org/10.1371/journal.pone.0080920.g001. From Mickleborough MJS, Chapman CM, Toma AS, Chan JHM, Truong G, et al. (2013) Interictal Neurocognitive Processing of Visual Stimuli in Migraine: Evidence from Event-Related Potentials. PLoS ONE 8(11): e80920. doi:https://doi.org/10.1371/journal.pone.0080920Copyright: © 2013 Mickleborough et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

4.3.5 Consistency with the Migraineur Experience

Do migraineurs report experiences that align with our conclusion? Although the ERP effects found are present in the absence of *clinically relevant deficits*, it may reflect a "vulnerability" to the cognitively demanding conditions of daily activities in patients with migraine [33]. Indeed, anecdotally, migraineurs often report on the distracting nature of extraneous visual inputs [1]. In fact, it is one of the first things migraineurs will tell us as participants in our attentional studies. For example, one migraineur reported that he found himself overwhelmed in large crowds, feeling as if he was pulled to attend to all the faces passing by him. Another participant complained of being unable to ignore the constant distraction of the moving captions on TV news channels. While these anecdotal examples fit with our conclusion that migraineurs have altered attention to irrelevant stimuli, they also underscore the lack of an empirical study comparing perceived attentional experience of migraineurs to controls.

While there is a lack of research on the migraineurs' perceived experience, several lines of empirical research are consistent with the conclusion that migraineurs have altered allocation of attention to extraneous visual stimuli. First, evidence indicates that migraineurs have difficulty extracting relevant stimuli from noise. Specifically, when detecting luminance targets in visual

noise resembling grainy photographs, Wagner et al. found that migraineurs have impairments in noise exclusion [39]. In addition, it is well established that migraineurs have difficulty identifying the direction of coherent motion in an incoherent environment [26, 40–43]. Specifically, migraineurs require a higher percentage of dots to be moving together than do controls in order to identify the global motion. Furthermore, migraineurs are found to be poorer at detecting a target when superimposed on a higher contrast mask [44]. Finally, the perception of visual stimuli is more difficult to suppress in migraineurs [45, 46]. For example, Chronicle and Mulleners used a TMS technique known as magnetic suppression of perceptual accuracy and demonstrated that migraine cortex is less proficient at suppressing letter stimuli [45]. Collectively, the research indicates migraineurs' ability to hone in on visual signals of interest is affected by increased distraction from extraneous noise.

4.3.6 Clinical Implications

Perhaps the most important remaining question is whether this research has real-world implications for migraineurs. In particular, to what extent might such information hold therapeutic value, both for day-to-day comfort and for decrease of actual migraine events? One can think of simple adjustments that a migraineur could make to limit distracting stimuli, such as sitting with a flashing television out of sight in a restaurant, studying with the door shut to avoid visual traffic, or sitting at the front of a classroom to avoid distractions from fellow students. From a more clinical standpoint, potential therapeutic training may help migraineurs to compensate for or overcome these attentional anomalies. For example, recent evidence suggests that action video-game playing leads to enhanced ability to suppress the cortical processing of distracting irrelevant visual information [47]. Specifically, the video-game players showed a greater suppression of cortical potentials to rapidly flashed sequences when attention was directed elsewhere. Given migraineurs' increased attention to irrelevant information and the potential for video-gaming to suppress this, one could imagine repetitive video-gaming or similar clinical training involving attention may have potential for reducing sensory-triggered migraine events.

4.4 Concluding Remarks

The research from this chapter suggests that migraine hyperexcitable visual cortex is not just a sensory issue, but that the consequences reverberate to attentional and cognitive processing between attacks. Similar to the sensory-cortical potentials, the most consistent result from the presented research suggests that overall migraineurs

show some level of enhanced cognitive potentials to both visual and auditory stimuli [27–30, 36–38]. This heightened state of cognition is consistent with what migraineurs anecdotally report about their daily experience with the distracting nature of visual and auditory extraneous inputs.

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Chapter 5
Sleep and Migraine

Morten Engstrøm and Jeanetta C. Rains

5.1 Introduction

Human consciousness changes regularly between different levels: awake and sleep with and without rapid eye movements (REM and NREM sleep). There is a biological regulation of these state changes that can be disturbed by habits and disorders (e.g., social jet lag or sleep apnea that reduce deep sleep or REM sleep). The importance of sufficient sleep is illustrated by the discovery of the glymphatic system, which cleans the brain for metabolites during sleep [1]. Neural/physical activity affects the need for sleep [2, 3] and can to some extent explain why sleep differs between individuals. Thus, the more energy used during awake time, the more important is the sleep time, but also the likelihood of high-quality sleep is found to be increased by physical activity [3]. In this way the homeostatic factor in sleep regulation appears logical. It also is quite intuitive why it is reasonable to have an inner clock regulating sleep that corresponds and adapts to Earth's rotation time (circadian factor). These two processes are also considered the most important for regulating sleep (Two Process Model) [4].

Extreme heterogeneity characterizes headache triggers, and sleep disturbances are among the most frequently mentioned migraine triggers [5–7]. However, it is

M. Engstrøm (✉)
Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway

Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
e-mail: morten.engstrom@ntnu.no

J. C. Rains
Center for Sleep and Pulmonary Medicine, Elliot Hospital, Manchester, NH, USA

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interesting that people with the same diagnosis could have different triggers and that people with different diagnoses, for instance, migraine and tension-type headache, could have the same triggers [8].

5.2 Clinical Perspective

Migraine is among other things related to stress, sleep disturbances, sleep deprivation, anxiety, insomnia, and daytime tiredness [9–18]. To perceive the mentioned factors as predisposing factors for a migraine attack fits with the notion that a migraine attack could be a genetically determined behavioral response orchestrated by the threatened brain [19]. Different people have different "Achilles heels", but for predisposed people, it is a situation of risk for a migraine attack when the strain is too high, and the rest is insufficient. Therefore, the migraine–sleep relationship is often described as bidirectional.

Migraine has been associated with a wide range of sleep disorders. Recent literature reviews have concluded that migraineurs, especially those with chronic and severe disorders, are at greater risk for insomnia, including adults [20] and children [21]. Studies of patients seen in neurology and specialty headache practices have identified insomnia in at least half of patients with migraine [22]. For example, in a clinical sample of 1283 migraine patients, 53% reported difficulty initiating sleep and 61% report difficulty maintaining sleep [9].

Some, but not all, epidemiological studies have supported the bidirectional relationship between migraine and insomnia. Sleep problems (fewer hours' sleep, fatigue, waking non-refreshed) were associated with poorer headache outcomes at the 12-year follow-up for tension-type headache but *not* migraine [23, 24]. Other epidemiological studies have found that insomnia increases the risk for later onset of headache and exacerbation of migraine [25–27], while pain, both muscle and skeletal and headache, increases the risk for insomnia problems.

Too little sleep is a risk factor for migraine, but low sleep quality might be more frequent [28]. Moreover, poor sleep also seems to increase the risk of headache chronification [29], and there seems to be a dose–response relation between insomnia symptoms and headache severity [25]. Even though a history of chronic insomnia does not predict poor objective sleep in all patients [30], insomnia symptoms sometimes also are connected to signs of increased sleep quality [31]. Thus, it might not solely be the sleep per se, but the high need for sleep, and even though sleep is good, the sleep might not cover the actual need.

So when migraineurs report reduced sleep quality compared to healthy controls [32], it could be a part of the stress state where insomnia or restless sleep predisposes for a migraine attack, but also the stress state increases sleep need and the impact of normal good sleep is insufficient. In this way stress and sleep could be partners in crime both in disorder pathophysiology and in triggering a migraine attack when the load sum exceeds the migraine trigger limit [33, 34].

An early chronotype and greater difficulty in coping with changes in sleep/wake schedule are found in migraineurs compared with controls (48.9% vs. 38.6%) [35], while evening-type patients seem to have more migraine attacks than morning types [36].

In a large telephone interview study about unspecified "chronic morning headache," circadian rhythm disorder was increased almost twofold in those with headache and more (OR: 2.6) in the subset of patients with daily headache [37].

Nocturnal awakening headache is a diagnostic symptom of sleep apnea headache, but interestingly, this symptom may, in fact, be more common in patients with insomnia than sleep apnea or snoring [38]. Headache, especially awakening headache, is more frequent among habitual snorers and obstructive sleep apnea patients than non-snorers. Across 12 studies, the prevalence of headache varied greatly from 18% to 60% of sleep apneics [39]. However, the degree and magnitude of the relationship are not known. A recent review of epidemiological research focusing on those more rigorous studies (e.g., physician-diagnosed headache and obstructive sleep apnea [OSA]) was not related to migraine or tension-type headache in the general population [40]. Even though an association between OSA and migraine, cluster and tension-type headaches seems clear in clinical reports [21, 41–44], the prevalence of OSA in unselected migraine patients presenting for treatment is unknown. Cluster [42, 45] and chronic daily headache refractory to conventional treatment [46] appear to be two clinical subgroups at high risk for OSA, especially in patients who have a body mass index (BMI) > 25 kg/m^2 [45].

Pooled analyses show that migraine is associated with restless leg syndrome (RLS) up to fourfold compared to healthy controls [47]. Across studies, migraine has been shown to be two- to fourfold more prevalent in samples of narcoleptic patients compared to controls [48–51]. There has been an elevated incidence of nightmares and non-REM parasomnias in migraine, especially among children, such as sleep bruxism, somnambulism, and night terrors [52–54]. Bruxism has also been found common in adults with migraine [55].

In line with Romberg's statement from 1853, "A migraine attack generally is closed by a profound and refreshing sleep" [56], resting also without sleep seems to be valuable [57]. The truth about sleep as medicine has to be nuanced as sleep itself or sometimes too much sleep is reported as a migraine trigger [17, 58]. Sleep-related headaches are also recognized as own diagnoses [59]. It is in line with common sense and experience that restless sleep could make many symptoms worse while restful sleep could alleviate and/or increase the capacity to deal with many symptoms. Migraine is probably not an exception.

As indicated above, it is difficult to understand how good relaxing sleep can induce headache if we do not hypothesize preceding exhaustion and that long sleep is not enough, a subsequent circadian rhythm disturbance or a sleep-disturbing factor worsened by sleep deprivation (e.g., sleep-related breathing disorder [60]). The optimal sleep is of sufficient duration, quality, and on the right time. However, if you feel bad when you wake up, it is probably not fair to always blame it on the sleep. Non-sleep disorders are also possible explanations and should be considered ruled out.

5.3 Anatomical and Physiological Perspective

The levels of serotonin (5-HT) seem to be disturbed in migraineurs [61–63], and 5-HT agonists are used as treatment for acute migraine [64]. In rats, sleep deprivation seems to increase the brain serotonin turnover [65]. At least short-time 5-HT reduction could reduce the diurnal sleep–awake rhythm [66]. 5-HT is among other things a precursor for melatonin—a circadian rhythm hormone [67]. In order to fall asleep, a disturbed circadian regulation could increase the demands of the homeostatic factor—which again could be a risk factor for both insomnia and migraine. Cerebral 5-HT secreting cells typically reduce their activity (along with norepinephrine) during sleep and increase their activity during awake [68]. It is not surprising that disturbances in this system may cause both migraine and sleep disturbances. However, the normal diurnal rhythmicity of levels of monoamines seems to decline by age [69], and this mechanism may then be less relevant.

A wave of increased cerebral activity followed by relatively long-lasting reduced neural activity, called cortical spreading depression (CSD), is a phenomenon that seems related to aura and headache [70–72] and seems to increase the need for sleep [73]. Increased neural activity increases the need for sleep [2], and reduced neural activity fits in itself with NREM sleep [74]. Animal experiments indicate that along with other metabolites, nitric oxide (NO) seems to increase in parts of the brain during sleep deprivation [75]. NO dilates blood vessels and glycerol trinitrate, which can deliver NO [76], and induces headache also in healthy controls [77, 78].

5.3.1 EEG and Polysomnography in Migraineurs

Sleep studies have documented abnormal sleep macrostructure and microstructure (i.e., cyclic alternating pattern [CAP, a system evaluating both fast and slow relatively short EEG phenomena]; K-complex sequences; delta bursts) in migraineurs, especially when migraine is chronic and/or ‘sleep related’—the specific subset of migraineurs for whom more than 50% of their headaches emerge during or following sleep (Table 5.1). In the 1970s, the earliest reports of polysomnography in migraine indicated headache onsets during sleep were more likely to occur during or subsequent to REM sleep [79–81]. The results are interesting but should probably be retested with more stringent methods.

Karthik et al. also found delayed sleep onset, decreased sleep time and efficiency, and decreased deep sleep in migraineurs [82]. Similar findings were later observed in children with severe migraine relative to those with mild to moderate headaches [83]; they also reported increased sleep-disordered breathing in migraineurs, compared to chronic migraine and nonspecific headache. In addition to the beforementioned review [40], a cross-sectional population-based study from the same group used the 4% desaturation criterion for hypopnea and could not detect increased prevalence of OSA in migraineurs [84].

Table 5.1 Overview of polysomnographic studies in subjects with migraine

First author, year	Design and numbers studied = *n*	Main results
Drake, 1990	Cross sectional, 10 with migraine, 10 TTH, and 10 mixed. Automatic sleep staging compared to normal values. Not evaluated statistical significance	Increased REM and REM latency
Vendrame, 2008	Retrospective analysis of PSG data from 90 children referred for headache: 60 migraine and 11 chronic migraine, 6 tension-type headache and 13 with nonspecific headache. No control group	Sleep-disordered breathing more frequent among children with migraine and nonspecific headache vs chronic migraine. Severe migraine was associated with shorter sleep time, longer sleep-onset latency, and shorter REM and SWS compared to mild/moderate migraine
Kristiansen, 2011	Blinded population-based cross sectional, $n = 431$	No association between OSA and migraine in the general population
Karthik, 2013	Cross sectional, 30 migraineurs without aura and 30 controls	Migraineurs had reduced sleep quality in PSG (sleep onset and efficiency, reduced NREM and sleep stage 4)
Engstrøm, 2013	Cross sectional, 50 migraineurs and 34 healthy controls	Interictal migraineurs had more awakenings. Preictal migraineurs had reduced sleep-onset latency compared to healthy controls
Nayak, 2016	Cross sectional, 25 migraineurs without aura and 25 healthy controls	Migraineurs had lower arousal index in REM sleep and a lower CAP rate than healthy controls
Verma, 2016	Observational, 50 patients with CTTH, 31 chronic migraine, 2 chronic cluster. No control group	No statistically significant polysomnographic differences in subgroups of chronic daily headache (no control group)
Sleep-related migraine		
Dexter, 1970	Repeated measures, $n = 7$, of whom 3 migraineurs	Nocturnal migraine might have a temporal relation to REM sleep
Hsu, 1977	Cross sectional, 15 of 33 sleep registrations were on migraineurs	More awakenings with migraine occurs from REM sleep or within 10 min of the end
Dexter, 1979	Repeated measures, 4 sleep migraineurs	Increased amount of deep (SWS) sleep and REM sleep before attack onset
Paiva, 1995[a]	Case reports, 25 participants complaining of predominantly nocturnal or morning headache (of whom 10 migraineurs)	After polysomnography, diagnoses were reevaluated. About 50% of the migraineurs got new diagnoses (e.g., obstructive sleep apnea, periodic limb movements)
Paiva, 1997	Case reports, 49 participants complaining of predominantly nocturnal or morning headache (unknown if migraine)	26 (55%) of the headache patients were diagnosed with a specific sleep disorder, and headache improved after treatment
Goder, 2001	Repeated measures, 8 migraineurs with attacks during sleep or upon awakening, of whom 7 migraineurs without aura	Reduced fast arousals in migraineurs with attacks related to sleep before an attack

(continued)

Table 5.1 (continued)

First author, year	Design and numbers studied = *n*	Main results
Della Marca, 2006	Cross sectional, 10 migraineurs with >50% of attacks during sleep and 10 controls	Reduced fast arousals in migraineurs with attacks related to sleep compared to controls
Engstrøm, 2013	Cross sectional, 15 migraineurs with headache start usually during sleep or upon awakening, 18 with non-sleep-related migraine and 34 healthy controls	NSM patients had more SWS and more K-bursts than SM patients and controls. SM patients had more awakenings and less D-bursts than controls
Vollono, 2013	Cross sectional, 8 with sleep-related migraine (>75% of attacks during sleep), 55 healthy controls	Reduced heart rate variability index—Low frequency/high frequency in N2 and N3 sleep and reduced CAP time and rate among migraineurs compared to controls. Higher pulse than controls awake and asleep except REM sleep

[a]Unspecified morning/nocturnal headache
SWS slow-wave sleep, *REM* rapid eye movement, *OSA* obstructive sleep apnea, *CAP* cyclic alternating pattern, *K-bursts* burst of K-complexes, *D-burst* burst of delta waves

5.3.2 Arousability

Overall, EEG among migraineurs is found to be normal or have subtle findings of drowsiness [85], while preictal symptoms [86] and shortened sleep-onset latency [87] fit with increased need for rest. Thus, it seems reasonable that both sleep disturbance [5] and thereby sleep deprivation could be worsening such state and be risk factors for migraine.

Digital EEG has enabled spectral analysis of sleep microstructure. Göder et al. analyzed the sleep microstructure of eight migraineurs and identified a reduction in arousals on nights preceding migraine [88], which might indicate increased sleep dept. Della Marca et al. analyzed the CAP in ten patients with migraine attacks related to sleep versus controls [89]. These migraineurs exhibited significantly lower arousal index in REM only, lower overall CAP rate (CAP duration/NREM sleep) and especially reduced low-frequency high-amplitude A1 bursts than normal. As both sleep-disturbing measures in REM and sleep-conserving measures in NREM were found abnormal, they hypothesized hypoactivity in the arousal system among migraineurs [90].

One study compared migraineurs with attack onset mainly during daytime with those with attack onset during sleep [31]. Migraineurs with attacks initiated during daytime were interictally found to have similar findings as sleep-deprived healthy people (increased daytime tiredness, increased slow-wave sleep, and reduced pain thresholds) even though they reported the same amount of sleep in their diaries. The findings were explained by increased sleep need compared to healthy controls. Innate increased pain sensitivity could possibly make the person more tired and increase the sleep need. The migraineurs with attack onset during sleep, however,

differed significantly. They had findings indicating sleep disturbance (more frequent awakening), but neither increased sleep-disturbing factors or increased daytime tiredness nor reduced pain thresholds. These findings could possibly be explained by a hyperactive arousal system with increased sensitivity for sleep disturbances, without subsequent reduced arousal (tiredness/sleepiness) in the daytime. Since increased arousability probably is related to increased blood pressure [91], hypertensive hypoalgesia [92] could counteract the normal reduction of pain threshold after sleep deprivation. However, blood pressure was not systematically compared in this study.

Abnormalities in biomarkers of autonomic function are reported by Vollono et al. [93]. Authors have evaluated heart rate variability among migraineurs compared to healthy controls and observed a reduced heart rate variability index among migraineurs. Sleep macrostructure or arousal index was not statistically different, but CAP rate was lower, indicating fewer slow EEG bursts among migraineurs. Migraineurs were also found to have higher mean heart rate awake and NREM sleep registration, but not during REM sleep. In principle, higher heart rate could be explained by poorer physical shape or a higher stress level among migraineurs during the test. A hyperarousal state is both in line with insomnia pathophysiology [94] and a state that theoretically could increase the sleep need. If so, the reduced heart rate variability could be a part of a constant higher stress level.

5.4 Therapeutic Perspective

Trigger management, including sleep education, establishing good sleep routines, and treatment of detectable sleep disorders, is of obvious importance to reduce headache attack frequency. If a patient has frequent headache attacks during sleep and sleep examination reveals a sleep disorder, isolated successful treatment and reduced headache frequency will confirm the migraine-triggering cause. However, if no sleep disorder is detected, there is a challenge. It might be correct to lower the diagnostic threshold for sleep disorders in these patients. Such approach consumes medical, economic and adminstrative resourses that must be weighed against the disadvantages of a possible disabling headache disorder.

5.5 Future Perspective

Clinical lore has long recognized the function of sleep in both provoking and relieving migraine. A sizeable literature has emerged demonstrating bidirectional effects of sleep disorders or processes and migraine. In recent years, science has provided a greater understanding of shared neurophysiology. Scientific advances have improved understanding of normal sleep processes, including circadian and homeostatic

regulation of sleep/wake; restorative functions of sleep, including the glymphatic system; and the pathophysiology of migraine. However, polysomnographic studies in migraineurs are relatively few. Most of them are small and of varying quality. The relation between headache, arousability, pain thresholds, and blood pressure should be clarified. High-quality, blinded studies with a sufficient number of participants are warranted. Such studies are resource demanding but absolutely necessary to confirm today's hypothesis or to get rid of the wrong ones.

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Chapter 6
Brain Oscillations and Migraine

Gianluca Coppola and Francesco Pierelli

Abbreviations

ACC	Anterior cingulate cortex
EEG	Electroencephalography
ERD	Event-related desynchronization
HFOs	High-frequency oscillations
LORETA	Low resolution brain electromagnetic tomography
MA	Migraine with aura
MO	Migraine without aura
rTMS	Repetitive transcranial magnetic stimulation
SS	Stead-state
SSEPs	Somatosensory evoked potentials
VEP	Visual evoked potential

6.1 Introduction

In an age where neuroimaging is indisputably the king of the tools used in research as well as clinical settings, neurophysiology still plays an important role not only in the diagnostic aspects of the disease but also, more importantly, in the assessment of physiopathological aspects of the disease. While neuroimaging has a better spatial resolving power, neurophysiology has a strong temporal resolution of milliseconds. The temporal resolving power increases further when the investigating

G. Coppola (✉)
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy
e-mail: gianluca.coppola@uniroma1.it

F. Pierelli
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy

IRCCS - Neuromed, Headache Clinic, Pozzilli (IS), Italy
e-mail: francesco.pierelli@uniroma1.it

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high-frequency oscillatory activity is embedded in both the spontaneous EEG activity and the multimodal evoked electrocortical responses. With the term *brain oscillations,* researchers commonly refer to "the rhythmic and/or repetitive electrical activity generated spontaneously and in response to stimuli by neural tissue in the central nervous system" [1]. Researchers from various medical disciplines have expressed a great deal of interest in this oscillatory activity, especially as it is very closely related to the subtle cognitive processes of the brain. Some frequency bands seem to be more related to the functional activity of regions deep in the brain, such as the brainstem and thalamus, while others are exclusively related to the activity of cortical pyramidal cells [2, 3].

However, the ability of brain cells to generate oscillatory activity is genetically determined [4] and is under the control of brain neurotransmitters, such as GABA, glutamate, serotonin, and dopamine [5–8]. Depending on the band of rhythmic activity and on the particular task, the oscillatory activity is characterized by a number of response parameters, such as amplitude, latency, desynchronization, coherence between different oscillations, and degree of entropy [1].

There are many neurological and psychiatric diseases that have benefited from the analysis of brain oscillatory activities: epilepsy, schizophrenia, dementias such as Alzheimer's, movement disorders, mood disorders, and so on.

In healthy humans, it is well recognized that marked changes in the cerebral rhythmic oscillatory activity over a wide range of frequency bands are related to pain processing [9, 10]. This also applies to the head pain associated with migraine, where brain oscillations have been studied extensively in the resting electroencephalogram (EEG), as well as in the underlying evoked oscillations that make up the evoked potentials (EPs) [11].

This chapter aims to provide a complete and systematic outline of the different neurophysiological studies based on the cerebral oscillatory activity of migraine patients along the various phases of its episodic cycle and even when it becomes chronic.

6.2 Resting-State Neural Oscillations

Despite the substantial ineffectiveness of the electroencephalogram recorded at rest in the diagnosis of migraine [12], which mainly remains clinical, several studies have used quantitative analysis of the electroencephalographic recordings showing abnormalities in the brain rhythmic activity, especially in the form of changes in the theta, delta, alpha, and beta rhythms.

As per the EEG recording, alpha total power decreased contralateral to the visually affected hemifield within 3 days of a migraine with aura (MA) attack, on the headache side in migraine without aura (MO), and up to the preictal phase in patients with menstrual-related migraine [13]. An increased total alpha power in a small subgroup of patients, with an excessive spread of alpha activity over either anterior

or temporal regions, was also observed in some studies [14, 15]. Nonetheless, a different study has confirmed lower EEG alpha power in migraine in comparison to controls using the low-resolution brain electromagnetic tomography (LORETA) localization method, especially in medial parts of the bilateral frontal cortex [16]. In an 18-channels EEG study, MO patients at rest and with eyes open showed lower delta, theta, alpha, and beta power in the fronto-central and parietal derivations during the interictal and ictal periods, while EEG power rhythmic variability in pre- and postictal periods was similar to that in controls [17]. In a blinded study which controls for the proximity of an attack, alpha rhythmic activity was found to be higher in variability during the preictal phase of migraine, and it increased in power during an attack as compared to the interictal recordings, particularly in patients experiencing intense photophobia [18]. Higher values of EEG power of alpha, as well as of delta, theta, and beta, frequency bands were also observed in a group of MO patients recorded during the preictal phase as compared to their interictal recordings [17].

Another common finding on an EEG in migraine is the excessive slowing [14]. Again, these abnormalities seem to vary in accordance with the time of an attack since the patients are most susceptible to an attack when the anterior EEG delta power and posterior alpha and theta asymmetry values are high [19].

A study recording alpha-band activity in the resting state before and after a psychophysical experiment observed that the migraine patients perform differently in the cognitive visual tasks between the attacks as compared with the healthy controls [20]. In another study, the power of resting-state alpha-band oscillations on EEG recordings was measured before and after a contrast discrimination task in a group of mixed migraine patients, with and without aura [21]. The migraine group as compared with the control group showed significantly higher average power for the lower (8–10 Hz) but not for the higher (10–12 Hz) alpha band before the contrast discrimination task, which increased significantly after the task only in the migraine group. There was no difference between the groups in equivalent internal noise estimates, which refers to random variability in the output of a system that originates within the system itself and is considered an indirect measure of background neural firing and signal quality [21].

6.3 Neural Oscillations Change as a Function of Sensory Load

Several experimental evidences have shown how the variations in amplitude, phase, and coherence of the alpha (8–12 Hz), beta (12.5–30 Hz), and gamma (30–45 Hz) frequency bands change as a function of sensory load. Spectral analysis allows to identify these frequency bands in the multimodal evoked potentials [22]. A few studies have investigated the alpha rhythm phase synchronization

phenomenon in a multichannel (18 electrodes) EEG evoked by repetitive visual stimuli (steady-state visual evoked potentials, SS-VEPs) in between the migraine attacks. These studies evaluated the synchronization index using Hilbert transform applied on all pairs of the scalp electrodes and observed increased alpha phase synchronization index between responses from different brain regions during an external visual stimulation, and not localized in a single region [23]. Since the alpha event-related synchronization and desynchronization (ERD) phenomena are regulated by the thalamic gating [24], the lack of ERD in migraine may be due to the malfunctioning thalamic filtering activity. In a subsequent study from the same group of researchers, EEG during flash stimuli was recorded by six scalp electrodes from 19 MO patients, 19 MA patients, and 11 healthy controls. In comparison with controls, an increased alpha phase synchronization after Hilbert transform was detected in MO between attacks, but not in MA, where instead a decreased beta band was observed. Moreover, the effective connectivity of alpha band by means of nonlinear Granger causality—as an index of cerebral functional connectivity—was found to be smaller in MO than in MA patients and controls. Compared with both MO and controls, MA patients showed higher Granger causality values in the beta band during visual stimulation [25]. All these neurophysiological indexes, however, were not related to the clinical features of migraine. To better understand the dynamic interactions between the brain areas and their modulation as a consequence of visual stimulation, groups of migraineurs with and without aura underwent a 65-channel EEG for networking analysis. During visual stimulation, the EEG pattern of MO patients was characterized by more segregated neural connectivity with smaller path length between the nodes and a greater clustering coefficient, and increased intrahemispheric global efficiency with respect to the MA patients, especially in the fronto-central areas. Besides, the EEG pattern of MA patients showed higher interhemispheric efficiency and increased centrality of connections in the parietal-occipital areas [26]. The biggest limitation of this type of study is the lack of a clear functional meaning of these electrophysiological measures in humans.

By borrowing a study paradigm widely validated with functional magnetic resonance imaging, some researchers recorded the 60-channel electroencephalographic activity in a group of patients suffering from migraine without aura evoked by a painful stimulus (ammonia) and a visual stimulus (binocular circular flickering checkerboard pattern, SS-VEPs) and observed that migraineurs had significantly higher alpha power in the cuneus during visual flickering as compared with the healthy controls. More intriguingly, the study also found significantly increased coupling of early visual areas with the left temporal pole, left anterior cingulate cortex (ACC), and right premotor cortex [27]. Nonetheless, the coupling strength between the cuneus and temporal/ACC significantly correlated with the number of days since the last attack. The authors did not find significant difference in nociceptive processing between the migraineurs and controls. The authors do not exclude the existence of differences between the migraineurs and healthy subjects in the subcortical brain structures, such as brain stem, thalamus, and hypothalamus, the

structures that are not accessible to conventional EEG [27]. More refined signal analysis techniques in recent times have made it possible to study the deepest cerebral activity of the migraine brain.

The application of a specific band-pass digital filter to broad-band somatosensory evoked potential (SSEP) recordings permits the extraction of a series of high-frequency oscillations (HFOs) with a mean frequency peak of 600 Hz. Multichannel source localization 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 fiber activity and primary cortical activation, respectively [3, 28]. Between attacks, the early component of the HFOs, but not the late component, was significantly smaller in migraineurs both with and without aura than in healthy subjects [29–34]. During a migraine attack the thalamocortical activity normalized, while the primary cortex activation remained stable [30] or increased in amplitude [32], with one notable exception where increased early HFO amplitudes during both the ictal and interictal periods of migraine were observed [35]. The electrophysiological pattern of normal thalamocortical activity and increased cortical oscillatory activity has also been observed in the patients who evolve from an episodic to a chronic form of migraine without medication overuse [32], suggesting that chronic migraine is a condition that resembles a "never-ending migraine attack" [36]. This neurophysiological pattern can also be obtained experimentally in the episodic migraine between attacks using the neuromodulation methods. In fact, some authors have been able to increase both early and late HFO amplitudes using high-frequency repetitive transcranial magnetic stimulation (rTMS) over the sensorimotor area, a technique to increase the cortical excitability. The usage of a lower frequency, inhibitory rTMS did not reach the same neurophysiological effect [31]. It is interesting to note that when sensorimotor cortical excitability is forcibly increased in episodic migraineurs, a reduction in the frequency and intensity of attacks may be induced [37], underlining a close relationship between the functional brain activity and the clinical manifestation of migraine.

The amplitude of early presynaptic HFOs is significantly correlated to the clinical evolution of migraine, since spontaneous worsening of the disease is associated with reduced early HFOs, whereas spontaneous improvement is linked with enhanced early HFOs [38]. No correlation was found between the amplitude of postsynaptic HFOs and clinical fluctuations. It is noteworthy that lower the amplitude of early HFOs, shorter the SSEP recovery cycle [39]—reflecting inefficient GABA inhibition—and higher the habituation deficit during the somatosensory stimulus repetition [40]. A close relationship was also noted between thalamocortical activity and lateral inhibitory activity in the somatosensory cortex in migraineurs during the interictal period, with an ictal normalization of the response. Both thalamocortical activity and lateral inhibition correlate with the severity of the attacks measured on a VAS scale [33].

Overall, these neurophysiological evidences are in favor of a close relationship between thalamocortical activity, the level of cortical responsiveness, and the severity of migraine disease.

6.4 The Thalamocortical Dysrhythmia Theory

Further evidence for reduced thalamic control of the sensory cortices in the migraine brain comes from the analysis of the oscillatory activity in the beta/gamma band (between 15 and 35 Hz) of the visual cortex in response to a checkerboard stimulus. The late (>100 ms post-stimulus reversal) oscillatory activity embedded in the common visual evoked potentials did not habituate to stimulus repetition between attacks in the patients with migraine with or without aura [41]. These results have been interpreted in the light of a dysfunction in the cortical oscillatory activity during the interictal period of migraine due to abnormal control by the thalamic pacemaker, so-called "thalamocortical dysrhythmia" theory, which was proposed as a cause for the emergence of positive clinical symptoms (referred to as the "edge effect") in several functional disorders of the brain [41, 42]. This syndrome is based on a change in the thalamocortical activity due to a morpho-functional disconnection of the thalamus from the brainstem that can result in an enhancement of low-frequency activity between the thalamus and cortex, which at the cortical level will diminish the lateral inhibition and augment phase-locked fast-spiking discharges in the inhibitory interneurons. The inclusion of migraine in this syndrome could reconcile the long-standing controversy between excessive excitation and reduced inhibition in migraine, as reduced thalamocortical activity leads to dysfunction of both inhibition and excitation (Fig. 6.1).

As a result of thalamocortical dysrhythmia, an altered degree of lateral inhibition was observed within the visual cortex of migraineurs during the pain-free period; it had significantly increased at the beginning of a series of stimuli as compared to the healthy subjects, but decreased, instead of increasing as in the healthy subjects, during late responses. This trend correlated with the cortical visual hyperreactivity (habituation) measured with common VEPs and with the number of days elapsed since the last attack [43]. A dysfunction of lateral inhibition mechanisms during the intercritical period was also detected in the somatosensory cortex by stimulation of two adjacent peripheral nerves at the wrist and again depending on the distance from the last migraine attack [33]. All these abnormal inhibitory activities normalized during an attack [33, 43]. These results favor a migraine cycle-dependent imbalance between excitation and inhibition in the sensory cortices that results in a cortical hyper-responsivity, that is, a deficient habituation to repeated stimuli. The fact that the early HFOs correlate with the degree of lateral inhibition of the somatosensory cortex emphasizes that migraine during its pain-free phase is characterized by abnormal thalamic control of the cortex [33], and furthermore, in a small group

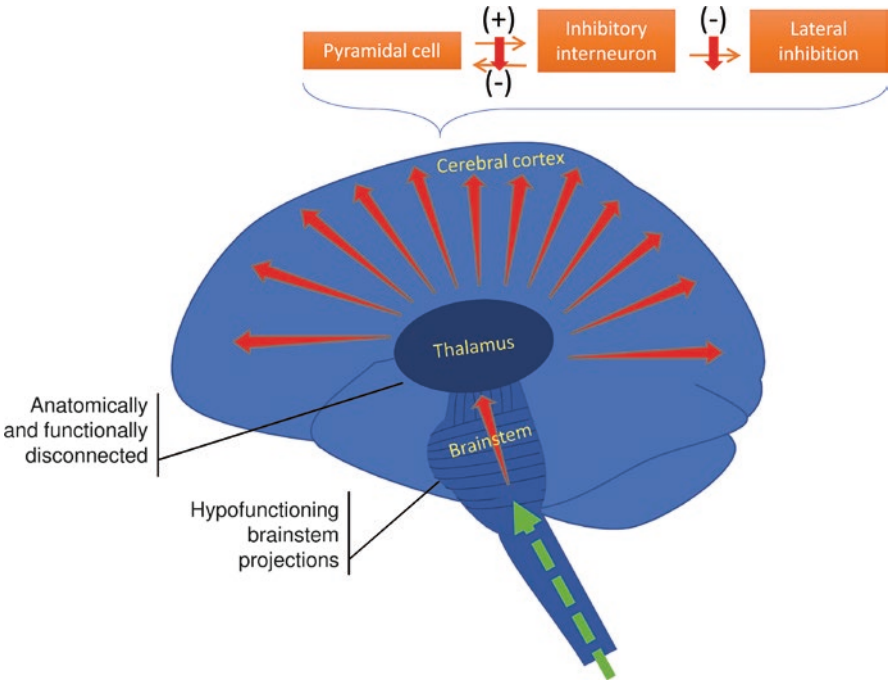

Fig. 6.1 Schematic representation of the anomalous path of sensory information processing in migraine during the interictal period. According to the model of thalamocortical dysrhythmia, in the presence of anatomical and functional abnormalities described in the brainstem structures of migraine, the thalamic nuclei are anatomically and functionally deafferented. These morpho-functional changes generate an abnormal thalamocortical rhythmic activity that results in a reduced activation of the pyramidal cells at the cortical level, which in turn activate the inhibitory interneurons less, thus not limiting the level of cortical excitability. A reduced inhibitory activity leads to a disinhibition of lateral inhibition mechanisms, which in the dysrhythmia model gives rise to the so-called "edge effect", the basis of functional disorders associated with the syndrome

of subjects, even paradoxical changes in the synaptic plasticity induced by rTMS are related to the thalamocortical activity [44].

Considering other thalamocortical dysrhythmia syndromes, we hypothesized that an interictal hypoactivity of monoaminergic pathways from the brainstem may cause a functional disconnection of the thalamus in migraine, leading to an abnormal intracortical short-range lateral inhibition, which could contribute to the habituation deficit observed during stimulus repetition [11] as well as aberrant paradoxical effects of rTMS [45, 46]. The reduced brainstem activation in migraine may cause a lower interictal thalamic/thalamocortical drive, which was confirmed by the analysis of high-frequency oscillatory activities in multichannel somatosensory evoked potentials [34]. Moreover, the application of a specific mathematical procedure called functional source separation to extract all the useful signal from the four nodes of the HFO somatosensory pathway, that is, the brainstem, the thalamus, and

two sensorimotor cortical sources, showed significant lower MO power values than healthy controls for the bilateral brainstem and thalamic sources, without any significant difference for the cortical sources [34]. Also, the study showed that lower the age of migraine onset, lesser is the amplitude power of the right brainstem and thalamic sources. In sum, this study provided evidence that low interictal thalamocortical drive in migraine can be due to genetically determined low brainstem activation, and not because of a primary cortical dysfunction [34].

Neurophysiological data can be used for reliably predicting the occurrence of episodic migraine attacks. In a recent study using a single-channel SSEP signal, classification tasks using machine learning approaches were performed [47]. The authors used broad-band evoked responses and HFOs to attain the discrimination between a relatively high accuracy of above 88% in migraine ictal or interictal versus healthy controls and above 80% in classification of migraine ictal versus interictal states [47].

6.5 Conclusions

Several clinical studies suggest that migraine patients have cyclic states characterized by abnormal processing of multisensory stimuli, which can be detected interictally. Functional exploration of the migraine brain has shown a number of electrocortical abnormalities, such as lack of habituation to evoked responses of multisensory modalities, response sensitization during the attacks and chronic migraine, and paradoxical responses to neuromodulation [11, 48]. Since the basis of both spontaneous and evoked brain activity is the sum of neuronal oscillatory activity at different frequencies (theta, delta, alpha, beta, gamma, and higher frequency bands), the study of these underlying signal components can help us to understand the genesis of the neurophysiological phenomena in the migraine brain.

The results obtained by analyzing the brain oscillatory activity during migraine can be summarized as follows (Table 6.1):

- The results from quantitative EEG are conflicting and inconclusive, as either reduced [13, 16, 17, 21] or augmented [14, 15, 17, 18, 21] alpha power was observed.
- Lack of ERD and increased alpha phase synchronization index and power amplitude in responses from different brain regions during external flash visual stimulation may be detected in between the attacks of migraine without aura [23, 25, 26]. Since the alpha ERD over the occipital-parietal areas after visual stimulation indicates a change from a resting to an activated state, lack of hypersynchronization pattern may be explained by a general malfunction of the thalamic gating effect [24]. This was not the case in migraine with aura patients, where instead decreased beta-band power was observed [25]. As beta oscillations have important functions in attentional state and in cognitive activity, their absence probably reflects defective cognitive attentional resources in MA [49].

Table 6.1 Synoptic table of neurophysiological changes, according to the frequency band, comparing episodic migraine with and without aura and chronic migraineurs

	Episodic migraine without aura	Episodic migraine with aura	Chronic migraine
Frequency band			
Delta	↑ of slow, ↑ asymmetry of anterior EEG delta power during the preictal phase		
Theta	↑ of slow, ↑ asymmetry of anterior EEG theta power during the preictal phase		
Alpha	↑ or normal amplitude during the interictal phase, ↑ phase synchronization, ↑ variability and amplitude during the preictal phase, ↓ effective connectivity of alpha band, ↑ coupling of early visual areas with the left temporal pole, ACC, and PMC	↑ interhemispheric efficiency and ↑ centrality of connections in the parietal-occipital areas	
Beta		↓ decreased beta band, ↑ effective connectivity of beta band	
Gamma	↓ habituation of late oscillatory activity		
HFOs	↓ thalamocortical activity between and ictal normalization, thalamocortical activity correlates to the clinical evolution of migraine	↓ thalamocortical activity	Normal thalamocortical activity and ↑cortical oscillatory activity

Arrows indicate the direction of change
EEG electroencephalography, *ACC* anterior cingulate cortex, *PMC* premotor cortex

- Another study showed that evoked alpha oscillatory activity fluctuates depending on the distance from the attack, as the strength of connectivity between the cuneus and the temporal pole/ACC increased with the number of days elapsed since the last attack [27]. A similar correlation with the number of days elapsed since the last attack was previously observed in migraine using common broad-band electrophysiology [33, 43, 50, 51], psychophysical tests [52], and neuroimaging [53–55].
- The analysis of high- and very high-frequency oscillatory activity underlying the common visual and somatosensory evoked potentials disclosed a reduced thalamocortical activity during the pain-free phase of migraine [29–32]. It was typical for the ictal phase, thus explaining the simultaneous normalization of the interictal neurophysiological abnormalities detected with the common broad-band multimodal responses [33, 43, 51, 56–58].
- An aberrant thalamocortical oscillatory activity may contribute to the determination of migraine clinical features, such as attack frequency and severity of headache [33, 38–40].

– Reduced brainstem activation in migraine may cause a lower interictal thalamic/thalamocortical drive, as confirmed from the analysis of high-frequency oscillatory activities in multichannel somatosensory evoked potentials [34].
– Reduced thalamic control of cortical processing may be responsible for both lack of sensory habituation [31] and paradoxical responses obtained after noninvasive brain neuromodulation, such as increased or decreased responses to inhibition or activation of transcranial magnetic stimulations, respectively [44, 46, 59].

In summary, a simultaneous dysfunction of the neuronal oscillations within the brainstem monoaminergic nuclei and the thalamocortical loop characterizes migraine between attacks. This abnormal oscillatory pattern is the hallmark of various functional brain disorders grouped under the name 'thalamocortical dysrhythmia' syndrome.

The aberrant cross-talk between the thalamus and cortex in migraine may contribute to abnormal connectivity patterns between cerebral networks, as recently shown with structural and functional MRI connectivity studies during [60] and between [61, 62] attacks. These abnormalities might be due to subtle plastic morpho-functional changes within the brainstem [55, 63] and thalamic [54, 64, 65] nuclei in migraine between attacks that seem to be dependent on the time point where patients are recorded during the migraine cycle [54, 55, 66].

However, the question remains as to what makes multisensory dysfunction unique to migraine and not to other types of pain. Further studies are necessary in order to compare the results obtained in migraineurs with other cephalic, extracephalic, acute, or chronic painful disorders.

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Chapter 7
Brainstem Reflexes

Catello Vollono

Brainstem structures play a critical role in the transmission of nociceptive impulses and in descending modulation of sensory transmission. Consequently, the study of brainstem reflexes may provide valuable insights into central pain processing mechanisms.

In this field, a large number of studies explored the brainstem by using reflex recording techniques (e.g., the trigeminofacial reflex, trigeminocervical reflexes, blink reflex, etc.).

Additionally, habituation and recovery curves to paired shocks, useful methods for investigating the excitability of the relevant sensitive, sensorial, nociceptive pathways in humans, were also widely evaluated for these reflexes. Since the trigeminal system and, more generally, the brainstem are key structures in the pathogenesis of migraine, the recovery curves of the aforementioned reflexes could provide valuable information about the status of the brainstem in this chronic pain disorder.

7.1 Exteroceptive Suppression of the Temporalis Muscle Contraction

Electrical stimulation of the infraorbital and mental nerves evokes a reflex that inhibits the voluntary contraction of the temporal and masseter muscles. A brainstem reflex mediates this inhibition, which is called "exteroceptive suppression." On surface EMG recordings of jaw-closing muscles, the reflex appears as two

C. Vollono (✉)
Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy

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suppression periods (SP1 and SP2) mediated by Aβ fibers: an early period, mediated by oligosynaptic pontine pathway, named SP1 response (ES1; 10–12 ms latency), and a late period, mediated by polysynaptic chain of interneurons of the lateral reticular formation, identified as SP2 response (ES2; 40–50 ms latency). The ES2 period is modulated via peripheral and central afferents (periaqueductal gray, nucleus raphe magnus, limbic cortex, orbitofrontal cortex). Consequently, the ES2 responses constitute a neurophysiologic correlate of the brainstem's level of excitability [1].

Temporalis exteroceptive suppression (ES) has been widely studied in investigations of pain mechanisms, motor control, trigeminal nerve function, basal ganglia disorders, and brainstem lesions [2–4].

Furthermore, recording of the ES2 period of jaw-closing muscle activity is the only standardized method of studying the function of the brainstem inhibitory interneurons [2, 5].

Despite its usefulness in the assessment of pain mechanisms, only few studies investigated the ES2 duration in migraine at rest, with contradictory results.

Schoenen et al. reported reduced exteroceptive suppression of the temporalis muscle in patients with chronic tension-type headache but normal latency and duration of exteroceptive suppression in migraineurs [1].

In another study, the same author detected abnormal shortening of ES2 suppression period in patients with migraine [6].

Other authors observed low degree (the area of suppression was measured and divided by its duration) of exteroceptive suppression in 17 patients suffering from migraine without aura, while exteroceptive suppression in patients suffering from migraine with aura and cluster headache was the same as that in normative subjects [7].

The low degree of suppression might be supposed to reflect a deficiency in the endogenous pain control mechanism [8].

Unlike the previous studies, Zwart et al. observed that the durations of ES1 and ES2 periods were within normal limits in migraineurs [9].

Another study showed no statistical difference in a group of 28 migraineurs during interictal phase, considering onset latencies and duration of ES1 and ES2 periods, compared with controls. In this study, however, shorter duration of the ES2 period was evident during the attack period [10].

The mechanism governing this loss of muscle contraction control in migraineurs is still unclear. The authors of this study hypothesized that in migraine there may coexist an abnormality of control mechanisms of vascular and muscle contraction, and thus, the pain sensation of attacks might produce psychologic stress resulting in the loss of the suppressive function.

Only one study also assessed the recovery curve of the ES2 component of the temporalis muscle activity [11]. These authors reported that latencies, durations, and recovery curves of ES2 did not differ between control subjects, migraineurs, and patients with episodic and chronic tension-type headache.

In conclusion, controversial results have been reported regarding the different inhibitory and excitatory responses detected by means of exteroceptive suppression of the temporalis muscle in patients with migraine.

In many papers, there are significant abnormalities in the responses obtained during the attacks and in the intercritical phase. Scientific data pointed to the hyperactivity of contralateral aminoergic cortical-subcortical pathways, whose function is decreased between the migraine attacks [12]. Thus, unilateral trigeminal system hyperactivity has also been suggested [13, 14].

In this view, the ES2 period of exteroceptive suppression of the temporalis muscle, an anti-nociceptive reflex, may reflect a deficit in the endogenous pain control mechanisms in different types of headache. It has been suggested, however, that this response could be useful as a biologic marker in monitoring the time course of recovery from pain [15], and it is sensitive during the pain-free interval, so it can detect the persistent interictal abnormalities in migraine.

For these reasons, some authors hypothesized that the latency of ES2 period may be helpful in the differential diagnosis of peripheral and primary headache disorders and in particular to differentiate migraine and tension-type headache [16].

Moreover, it is conceivable that the exteroceptive suppression of the temporalis muscle may be used for evaluation of a drug's effect. In fact, part of the 5HT effects in migraine is related to the inhibition of the trigeminal nuclear activity, and it is probable that part of the triptans effects is also mediated at this central site [17].

7.2 Trigeminocervical Reflexes

The trigeminocervical reflex (TCR) is obtained from the resting sternocleidomastoid muscle, using surface electromyographic recordings. Surface electrodes are positioned in a longitudinal direction over the muscles. Electrical stimuli are applied bilaterally to the supraorbital trigeminal branch near the point of nerve exit from the skull. The intensity is modified in order to result as strong but not painful. Several consecutive responses are averaged in each trace. The onset latency (ms), duration (ms), peak-to-peak amplitude (mV), and area (mV × ms) of the reflex responses are measured [18].

The trigeminocervical reflex, utilizing connections from the face to the neck motoneurones, is used for the examination of the brainstem interneuronal activity and its central control [18]. It may be supposed that different brainstem interneurons control the trigemino-trigeminal and the trigeminocervical reflexes.

Some authors used this neurophysiologic examination to assess brainstem interneurones function in migraine.

In one of the oldest studies assessing TCR [18], on the painful side of migraine patients, the mean onset reflex latency after ipsilateral and contralateral stimulation

was strongly shortened. Conversely, there were no significant differences in the reflex duration, area, and amplitude between the painful and non-painful sides. No differences were also found between migraineurs and patients with tension-type headache [18]. The results of this study suggest a decreased activity of the brainstem inhibitory interneurons in migraine.

Other authors explored interictal and ictal phases of migraine. In particular, Nardone et al. [19] found that trigeminocervical responses are bilaterally abnormal in 17 out of 20 patients with migraine with aura (MA) and 15 out of 20 patients with migraine without aura (MO) during the headache attacks. In half of MA and MO patients, there were abnormal responses also during the interictal period. Moreover, in patients with normal trigeminocervical responses during the pain-free phase, the triptans were significantly more effective at relieving headache [19].

These findings were confirmed in another study by the same authors [20] and are consistent with the central role of the trigeminal system in the pathogenesis of migraine. The bilateral location of the abnormalities suggests a centrally located dysfunction. In particular, the trigeminocervical reflex is sensitive in disclosing a disordered brainstem activity and may be an index of neuronal activity in the human brainstem; moreover, its assessment may help as a valuable prognostic tool for predicting the efficacy of triptans therapy [20].

Partially in contrast with previous results, other authors [21] found no changes between controls and high-frequency episodic MO and MA patients in the mean values of trigemino-cervical-spinal reflexes (TCRSs) obtained at rest and during heterotopic painful stimulation (cold pressor test). Furthermore, the recovery curve of TCRs was significantly and markedly faster in migraine patients than in controls, while no differences were found in the basal trigemino-spinal reflexes (TSRs) [21]. The authors conclude that the interictal period of migraine is characterized by a hyperexcitability of the trigeminal pathways and by their anatomical and functional connections with the upper cervical cord neurons.

In conclusion, the trigemino-cervical and the trigemino-cervical-spinal reflexes may be useful for the evaluation of the impairment of the brainstem neuronal networks in migraine patients.

Overall, the more relevant findings of these studies demonstrated an abnormal hyperexcitability of trigeminal system during interictal phase, apparently not linked with supraspinal inhibitory modulation.

The “abnormality” of the supraspinal influences is probably more significant during the migraine attack and in the chronic migraine form than during the pain-free period.

TCR and TCRS studies are of little use in the diagnosis but are helpful for a better understanding of the common pain control mechanisms and the pathophysiology of migraine. In particular, the study of the recovery cycle of these reflexes appears to be a technique that can be used to make an accurate functional evaluation of the trigeminal pathways.

7.3 Blink Reflex

The mechanical or electrical stimulation of the supraorbital nerve elicits "blink reflex" responses and resembles the corneal reflex tested in clinical evaluation [22–24].

Usually, for the purpose of studying blink reflex, surface recording electrodes are located on the lower lateral side of the orbicularis oculi, reference electrodes are positioned on the lateral surface of the nose, and the ground electrode is located around the arm. The supraorbital nerve is stimulated with the cathode placed over the supraorbital foramen. Stimulation rate is 1 s^{-1}. The shortest latency is taken into account and the EMG is not rectified.

Stimulation of the supraorbital nerve elicits two temporally separate responses of the orbicularis oculi, an early (R1) component, and two temporally separate contractile late responses ipsilateral and contralateral to the stimulation (R2 and R2′, respectively). R1 is an oligosynaptic reflex response and is evoked only on the side of stimulation via a pontine pathway [22–24]. On the other hand, unilateral stimulation elicits R2 bilateral response, which is presumably relayed through a more complex route (polysynaptic), including the pons and lateral medulla [25–28].

So, the blink reflex can be an objective and useful method for studying brainstem and the trigeminal system. Blink reflex recordings provide, consequently, a quantitative analysis for functions that involve the fifth and seventh cranial nerves, the dorsolateral pons, and the lateral medulla.

Several studies compared the latencies of R1, R2, and R2′ waves in migraine patients and control subjects (Table 7.1).

In the oldest study that evaluated blink reflex in 43 migraine patients, Bánk et al. [29] obtained the same R1 latencies in migraineurs and controls but R2 latency significantly prolonged in the migraine group. These findings indicate that trigeminal afferents and/or polysynaptic pathway in brainstem may be slightly functionally altered in migraine. The reasons for this delay are uncertain, especially in a headache-free interval.

This slight functional brainstem abnormality may underline or be the basis of migraine susceptibility. On the other hand, a peripheral abnormality of the trigeminal afferents could play a part in these pathophysiologic mechanisms. Sensory deficits of the face often can cause R2 latency alteration.

Other authors [30] reported that there was a statistically significant extension of bilateral R2 latencies in a 40-migraineur group compared with TTH patients and control groups. These confirm that brainstem and trigeminovascular connections play an important role in migraine pathogenesis and are functionally impaired in migraineurs (trigeminal system activation, sensitization of brainstem trigeminal nucleus, abnormal synaptic transmission, suppression of brainstem interneuron region) [30].

Table 7.1 Blink reflex in migraine

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Conventional blink reflex					
Bánk et al. [29]	43	33 MO, 10 MA	31.1 (9.6)	>14 days after attack	R2 latency prolonged in migraine
Sand and Zwart [31]	11	10 MO, 5 MA	39 (12)	NA	No differences compared to controls
Avramidis et al. [38]	19	MO	37.5	Ictal	R2 amplitude reduced ictally. Sumatriptan subcutaneous increased R2 amplitude
Aktekin et al. [11]	20	MO	32.7 (8.5)	Interictal	No difference compared to controls and TTH
De Tommaso et al. [49]	35	25 MO, 10 MA	MO 33.5 (4.5) MA 37.8 (6.7)	Interictal	R3 threshold, with a normal pain threshold, in migraine patients. R2 and R3 components less influenced in patients compared with controls
De Marinis et al. [32]	30	MO	33 (8)	>72 h after attack	No baseline responses differences
Sand et al. [34]	23	13 MO, 10 MA	33.9 (12.5)	NA	No difference compared to controls
De Marinis et al. [33]	35	CM	37 (6)	>72 h after attack <3 hours before the next attack	No difference compared to controls
Yildirim et al. [30]	40	25 MO, 15 MA	33 (18–64)	Interictal	Extension of bilateral R2 latencies
Brooks and Fragoso [36]	160	CM	50.8 (18.2)	NA	No difference compared to controls
Uygunoglu et al. [35]	20	6 MO, 14 CM	37.5 (8.9)	Within 48 h after attack	No difference compared to controls
Nociception-specific blink reflex					
Kaube et al. [39]	17	MO	40 (24–56)	Interictal, <6 h, after migraine attack onset and after Zolmitriptan	Decreased R2 latencies during acute attack compared with the headache-free interval, most pronounced on the headache side
Katsarava et al. [42]	14	MO	36 (24–56)	Interictal, < 6 h, after migraine attack onset and after Zolmitriptan	Increased R2 amplitude and decreased latency on the pain side during attacks only in migraine patients

Table 7.1 (continued)

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Ayzenberg et al. [37]	45	16 MO, 29 CM	MO 37.4 (12.2) CM 40.1 (14.1)	Outside of a migraine attack	No difference between MO, CM, medication overuse headache and controls
Coppola et al. [43]	14	MO	30.7 (9.3)	Interictal, >3 days after attack <3 days before the next attack	No difference between patients and controls
Sohn et al. [44]	68	38 MO, 30 CM	MO 40.1 (10) CM 43.1 (11.1)	Interictal	Episodic migraine patients: Decreased latencies, larger amplitudes and area-under-the-curve (AUC) values for the R2 component. Chronic migraine patients: Prolonged latencies, smaller amplitudes and smaller AUC values for the R2 response
Perrotta et al. [48]	46	29 MO, 17 MA	MO 37.3 (10.6) MA 34.5 (10.9)	Interictal	No significant differences at baseline
Williams et al.	23	MO	24.32 (7.94)	Interictal	No difference of baseline nociceptive BR magnitude compared to controls
Habituation					
De Marinis et al. [32]	30	MO	33 (8)	>72 h after attack	No baseline responses differences. Blink reflex habituation markedly reduced in who had and attack within 72 h
Katsarava et al. [45]	17	MO	40 (24–56)	Interictal and within 6 h of onset of attack	Habituation deficit interictally. Difference of habituation between and during attacks Increased R2 amplitude interictally No difference between headache and non-headache sides
Di Clemente et al. [46]	15	MO	28 (10)	Interictal, > 2 days after attack <2 days before the next attack	Nociception-specific blink reflex. Decreased habituation in migraine patients

(continued)

Table 7.1 (continued)

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Di Clemente et al. [47]	16	MO	27.6	Interictal, > 2 days after attack <2 days before the next attack	Nociception-specific blink reflex. Habituation deficit in migrainepatients, inversely related to attack frequency
De Marinis et al. [33]	35	CM	33 (8)	>72 h after attack	No baseline responses differences. Significant lack of blink reflex habituation in chronic migraineurs interictally vs ictally and vs controls
Coppola et al. [43]	14	MO	30.7 (9.3)	Interictal, > 3 days after attack <3 days before the next attack	Nociception-specific blink reflex after conditioning stimulus. No basal BR difference between patients and controls. BR recovery curves were normal in MO patients compared to healthy controls
Perrotta et al. [48]	46	29 MO, 17 MA	MO 37.3 (10.6) MA 34.5 (10.9)	Interictal	Frequency-dependent deficit of habituation of nBR R2 in both MO and MA patients, less clear in MA. Positive correlation between the habituation rate and migraine frequency in MO

MO episodic migraine without aura, *MA* episodic migraine with aura, *CM* chronic migraine

Unlike previous studies, Sand and Zwart [31] reported that mean R1 and R2 latencies were no different between various headache groups and that no group differences were found for the contralateral R2 response.

These findings were completely confirmed by Aktekin and colleagues [11] in episodic migraineurs. In this population, in fact, no differences were found also considering the facial side explored.

Some other researchers found normal R1 and R2 latencies, amplitudes, and areas obtained by ipsilateral and contralateral stimulations at any time intervals, during interictal phases of migraine as well as in episodic [32] and chronic migraine [33].

Other studies confirmed that there are no differences in all blink reflex components in migraine without aura, migraine with aura patients and controls and unilateral migraine patients did not differ from patients with bilateral pain [34, 35]. No significant differences were reported in another large group of migraine patients [36] and in medication overuse headache patients [37].

Avramidis et al. [38] reported similar results during interictal phase in 19 episodic migraineurs. In particular, latencies of all components are normal in all migraineurs. Conversely, during headache phase, significantly lower values of R2

and R2′ amplitude and size were found in the migraine group compared with the healthy control group. These findings were independent from stimulation site and were altered in the symptomatic side of headache. These authors described, furthermore, that sumatriptan administration was able to normalize R2′ amplitude and size.

The interpretation of these findings is that there is a temporary dysfunction of the bulbo-pontine interneurons only during the headache phase of migraine. In particular, the brainstem interneuron, which is part of the blink reflex arc, may be diffusely suppressed in migraine, only during the headache phase. Besides, blink reflex may be an objective laboratory method to monitor the effectiveness of specific drugs proposed for the treatment of migraine.

Other authors studied the blink reflex during migraine attacks.

Kaube et al. [39] studied 17 episodic migraine patients with unilateral migraine headache. The patients were studied within 6 h of attack's onset. Blink reflexes were elicited in all patients using two different electrodes, a standard stimulating electrode (standard blink reflex) and a novel concentric stimulating "nociception-specific" electrode ("nociception-specific" blink reflex), during the acute migraine attack and after the treatment with intravenously lysine acetylsalicylate (1 g) or oral zolmitriptan (5 mg). The same protocols were used interictally. After "standard" stimulation, no differences were detected for the R1 and R2 onset latencies and areas under the curve (AUC) between the different time points and between the headache and non-headache side. "Nociception-specific" stimulation revealed, however, a significant shortening of R2 latency during the acute migraine attack compared with the headache-free interval. Drug treatment relief increased the onset latencies and reduced the AUC of R2 [39].

The authors of this study suggest a temporary sensitization of central trigeminal neurons during acute migraine attacks. In fact, the decrease of the onset latency and increase of the reflex integral (AUC) permit to hypothesize a facilitation of a spinal or medullary reflex. These findings are consistent with other experimental data [40].

These results are probably evident in this study and not in other similar studies because of a more selective stimulation ("nociception-specific") that may lead to a higher and near-maximal saturation of the afferent pathway of the blink reflex and a reduced sensitivity toward more subtle changes in central thresholds and gain in sensory trigeminal transmission [41].

Another study confirmed these findings [42]. In this study, the comparison of R2 onset latencies during pain and during pain-free period within the groups of patients with migraine and sinusitis revealed a significant decrease of R2 latencies during the migraine attack compared to pain-free period but no differences between pain phase and pain-free period in the group of patients with sinusitis. These results are consistent with the facilitation of trigeminal nociception that seems specific for migraine rather than a consequence of peripheral pain, such as frontal sinusitis [42].

Other authors assessed the "nociception-specific" blink reflex interictally. Coppola et al. [43] reported no difference between migraineurs and healthy subjects

for nociception-specific blink reflex (nBR) R2 responses in terms of stimulus intensity, pain threshold, onset latency, or AUC ipsilateral and contralateral.

Another study [44] showed that episodic migraine (EM) patients presented significantly decreased latencies and larger amplitudes and area-under-the-curve (AUC) values for the R2 component, whereas chronic migraine (CM) patients showed significantly prolonged latencies, smaller amplitudes, and AUC values for the R2 component. In the same study, the patients were assessed by means of pain-related evoked potentials (PREP) and both the EM and CM patients had decreased latencies of PREP responses with larger amplitude compared with the controls, which indicates facilitation at the cortical level. Additionally, the amplitude and AUC values of the R2 component exhibited a negative correlation, whereas the latency of the R2 component for the nBR showed a positive correlation with the frequency of headaches in migraineurs. This study provides electrophysiologic evidence that excitability of nociceptive-specific trigeminal pathways is different between EM and CM [44].

Other authors [37] assessing simultaneously nBR and PREP found "facilitation" of both trigeminal and somatic PREP, but not of nBR, indicating that the sensitization of nociceptive mechanisms mainly involved structures external to the trigeminal system and probably occurred at the supraspinal level [37].

In addition to the basal assessment of both "classical" and "nociception-specific" blink reflexes, many authors have compared the "recovery curve" and the habituation of blink reflex of migraineurs to non-migraine subjects.

Aktekin et al. reported similar R2 recovery curves in migraineurs and controls [11].

Coppola et al. confirmed these results [43] and described no difference of the nociceptive-BR R2 recovery curves between migraine patients outside of attacks and healthy volunteers.

De Marinis et al. [32] found R1 and R2 latencies, amplitudes, and areas similar in patients and control subject during basal assessment, but blink reflex habituation responses (R2 areas obtained at subsequent time intervals ranging between 10–5, 5–4, 4–3, and 3–2 s) markedly and statistically reduced in migraineurs with migraine attack within 72 h after neurophysiologic evaluation. In fact, in the comparison between groups, the R2 areas progressively decreased in control subjects, but remained high in migraine patients who experienced an attack within 72 h after testing. Also, the blink reflex habituation responses of the patients who had migraine attack after a longer time interval (from 4 to 15 days) were found reduced but did not differ significantly from those of controls. No correlations were found between blink reflex responses and age, duration of disease, and side of pain. These data are consistent with the activation of brainstem pathways involved in the blink reflex in the premonitory phase of migraine attacks, probably through mechanisms that involve dopaminergic function [32].

These findings confirmed the results of another contemporary study [45] that reported a significant defective habituation of blink reflex responses in patients

during interictal period, fully reverted and "normalized" during a migraine attack [45].

Also Di Clemente et al. [46] found significant habituation deficit of BR-R2 response area in patients with migraine without aura during interictal phase. This lack of habituation shows a positive correlation in the same patients with a cortical habituation deficit, namely, the habituation of pattern-reversal visual evoked potentials.

These authors conclude that there is a wide neurobiologic dysfunction responsible for the habituation deficit in both cortex and brainstem [46].

The same authors investigated a nociceptive BR in 16 migraine patients without aura, 15 healthy subjects, and 14 healthy subjects with family history of migraine in their first-degree relatives [47]. The most significant habituation impairment was found in healthy subjects with a family history of migraine. The second one was found in migraine patients without aura, inversely correlated with the frequency of attacks. The authors interpreted that these results are the consequence of reduced serotoninergic transmission, leading to a decreased preactivation level, and are not due to trigeminal sensitization. Finally, an insufficient nociceptive-specific BR habituation is probably a presymptomatic neurophysiologic abnormality and, in this view, a marker of genetic predisposition for migraine [47].

In another study, De Marinis et al. [33] investigated the BR habituation in 35 patients with chronic migraine, outside and during a spontaneous attack, and control subjects. The habituation responses, delivered at time intervals of 10, 5, 4, 3, 2, and 1 s, were markedly reduced in patients studied outside an attack compared with those of the same patients studied during a migraine attack and of those of control subjects. There was a significant correlation between the decreased habituation of the blink reflex and a higher frequency of attacks. The decreased BR habituation outside an attack reveals abnormal excitability in chronic migraine, which normalizes during the attacks. The authors explain these data with central sensitization mechanisms that may also cause lower detection thresholds on the side affected by headache in patients during the attacks (allodynia). The blink reflex and its habituation may help shed light on the subtle neurophysiologic changes that occur in migraine patients between and during attacks [33].

A recent study [48] has confirmed that both migraine without aura and migraine with aura subjects showed a clear frequency-dependent deficit of habituation of the nBR-R2 responses when compared to healthy volunteers. However, migraine with aura subjects showed a less marked and/or non-homogeneous significant deficit of habituation of the nBR-R2 when compared to healthy controls. Furthermore, only in migraine without aura subjects, the mean frequency of migraine attacks correlates positively with the habituation rate of the nBR-R2. Based on these slight differences in terms of habituation deficit, the authors speculate a modulating role of the migraine aura susceptibility and excitability of the nociceptive trigeminal pathways [48].

Several authors also studied the effect of preceding conditioning stimuli on a blink reflex.

De Tommaso et al. [49] described a slight increase of blink reflex responses recovery after preconditioning stimulus observed in migraine patients.

Also Coppola et al. [43] reported that the inhibition of nBR obtained by means of supraorbital or peripheral (index finger) conditioning stimulation is normal in migraineurs interictally, which does exclude the previous hypothesized persistent sensitization in the trigeminal nociceptive system and demonstrate that descending brainstem pathways on medullary R2 interneurones are normal in migraine between attacks [43].

A more recent article [35] has reported that one-third of migraine patients did not have prepulse inhibition of R2 response after conditioning stimulation of the median nerve at wrist. These authors conclude that in migraine there is a loss of sensory modulation at the level of brainstem during and immediately after the attacks.

Other authors [50] reported that migraineurs did not have a significant change in nBR magnitude during a conditioning setting (noxious counterstimulus applied by inducing forearm ischemia), suggesting impaired conditioned pain modulation and, consequently, a deficient inhibition of trigeminal nociception.

In contrast to the evident lack of habituation found in the majority of studies assessing blink reflex responses in common migraine, this deficit is not present in genetic forms of migraine.

In fact, Hansen et al. [51] found that nociceptive BR habituation increased more in familial hemiplegic migraine (FHM-1 and FHM-2) subjects than in subjects with common migraine and controls. These results indirectly suggest that hyperexcitability of cortical neurons, previously demonstrated in the animal model of the FHM-1 and FHM-2 mutations in transgenic mice [52, 53], is not per se responsible for the habituation deficit in the common forms of migraine. Alternatively, in FHM, an increase in cortical inhibitory mechanism might compensate between attacks for the genetically determined increased neuronal excitability. All these results support the concept that various pathophysiologic aspects differ between FHM and common migraine, including cortical and brainstem responsiveness.

Lastly, several authors reported a clear effect (significant modification of blink reflex assessment's findings) of different substances and pharmacologic and non-pharmacologic treatment of migraine [39, 54–57].

A recent paper [58] has reported an interesting different effect of ketogenic diet on cortical and brainstem habituation responses.

Also, low-frequency short-time stimulation of the greater occipital nerve seems not to modify nociceptive blink reflex responses [59].

In conclusion, most of the studies assessing blink reflex in migraine show substantial normality of the findings obtained from basal BR recordings in patients and, in many cases, significant and sudden variations of the response patterns only in the periictal phase.

In most of the studies that evaluated habituation and/or conditioning, larger differences are evident in terms of response patterns between migraine and

non-migraine subjects. Such habituation anomalies, in almost all the studies, revert in the ictal phase.

The variability of the results in the study of blink reflex in migraine by many authors is a consequence of a series of factors: frequency of crises, proximity of the last crisis or of the next one, side predominance, stimulation modality, and prophylactic treatment.

Therefore, the blink reflex studies demonstrate the dynamic and sudden recurrent unbalance of excitability of all CNS systems (cortical, subcortical, brainstem, hypothalamus, and trigeminal structures).

This unbalance is more evident cyclically near or during a migraine attack, when the habituation deficit normalizes and sensitization of the pain pathways increases.

Finally, BR studies are a suitable tool for testing a drug's efficacy.

7.4 Auditory Evoked Potentials

Auditory stimuli elicit small electrical potentials can be distinguished into short-, middle-, and long-latency auditory evoked potentials (AEPs), based on their generators in the auditory pathways. Short-latency AEPs originate in brainstem; conversely, middle- and long-latency AEPs originate in the auditory cortex.

For clinical and research studies, a set of five recording channels is recommended, including electrodes Fz, Cz, F3, and F4 of the international 10–20 system, referenced to the linked mastoid processes, but this is rarely conceivable in clinical practice, as many evoked potential recording devices offer no more than two recording channels. Averaging should be performed after an artifact rejection and should include at least 200 responses per condition.

AEPs are a sensitive measure of central nervous system dysfunction [60, 61], particularly of the brainstem. However, the studies of these potentials in migraine has yielded contradictory results [62–64] (Table 7.2).

Studies of short-latency AEPs, that is, brainstem auditory evoked responses (BAER), provide varying and heterogeneous results in migraine. Normal latencies [62–66]; increased latencies, especially for wave V [67, 68] mostly during the attacks [62, 65]; and interaural asymmetries [67], particularly in migraine with aura [69] were reported. An inverse correlation between discomfort to stimulations of low intensity (55 dB) and wave IV–V amplitude was found in another study [66].

The rare studies of cortical long-latency auditory evoked potentials showed no significant difference between migraineurs and controls with regard to N1, P2, and N2 component latency or amplitude [68].

Another recent study has confirmed no difference in terms of latency, amplitude, and interpeak of all auditory brainstem components between a group of vestibular migraine and control subjects. The same authors, however, found increased

Table 7.2 Auditory evoked potentials in migraine

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Short latency					
Benna et al. [64]	10	MO	36 (25–46)	>8 days after attack	No abnormalities or asymmetries compared to controls
Bussone et al. [67]	20	MO	36.4 (9)	>1 week after attack	Increased and asymmetric I–V latencies in migraineurs
Yamada et al. [65]	1	MA (basilar migraine)	38 (–)	Interictal and ictal	IV and V wave latencies prolonged during headache
Podoshin et al. [62]	17	10 MO, 5 MA	36.7 (11–61)	Interictal and ictal	No interictal differences compared to controls. Prolonged interpeak latencies during headache
Battistella et al. [63]	28	23 MO, 5 MA	12 (2)	>1 week after attack	No difference compared to controls
Schlake et al. [69]	38	19 MO, 19 MA	32.4 (12.4)	Interictal	Asymmetric I, II, III and V latencies in migraineurs (especially in MA)
Drake et al. [68]	50	MO	(16–67)	NA	Prolonged I–V and III–V interpeak latencies in migraineurs compared to controls
Sand and Vingen [66]	21	15 MO, 6 MA	39.3 (9.2)	>3 days after/ before attack; 'pre-attack group': Attack within 24 h	No difference compared to controls
Takeuti et al. [70]	29	Vestibular migraine	49.7 (23.7)	Interictal	No difference in latency, amplitude and interpeak of all components compared to controls. Increased latencies of the frequency following response and lower discomfort thresholds compared to the control group
Middle latency					
Ambrosini et al. [73]	20	MO	32.5 (21–62)	3 days after the last and before the next attack	Auditory P50 response was markedly reduced in migraine patients compared to healthy volunteers
Long latency					
Drake et al. [68]	30	MO	29 (17–54)	NA	No difference compared to controls
Sand and Vingen [66]	21	15 MO, 6 MA	39.3 (9.2)	>3 days after/ before attack; 'pre-attack group': Attack within 24 h	No difference compared to controls

Table 7.2 (continued)

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Intensity dependence AEPs					
Wang et al [77]	26	MO	28.8 (6.4)	>1 week after attack	Enhanced intensity dependence of N1-P2 in migraineurs
Judit et al. [76]	77	69 MO, 8 MA	34	1 day before attack, during attack, 1 and 2 days after attack, interictal	Enhanced intensity dependence of auditory evoked potential interictally and dramatic reduction just before and during the attack
Siniatchkin et al. [79]	16	MO	10.6 (7–13)	NA	IDAP parameters enhanced in migraine
Sándor et al [78]	26	24 MO, 2 MA	30.9 (14.4)	3 days after the last and before the next attack	IDAP parameters enhanced in migraine
Ambrosini et al. [80]	328	232 MO, 96 MA	35.3–34.4	3 days after the last and before the next attack	Intensity dependence of auditory evoked cortical potentials is increased during interictal phase of migraine
Habituation					
Wang et al. [71]	35	25 MO, 10 MA	36–37	>1 week after attack <5 days befor attack	Potentiation of N1–P2 amplitude only at high stimulus intensities
Sand and Vingen [66]	21	15 MO, 6 MA	39.3 (9.2)	>3 days after/ before attack; 'pre-attack group': Attack within 24 h	No difference compared to controls
Ambrosini et al. [72]	14	MO	31.2 (19–62)	3 days after the last and before the next attack	Potentiation in migraineurs, greater for high- than for low-intensity stimulations

MO episodic migraine without aura, *MA* episodic migraine with aura

latencies of the frequency following response and lower discomfort thresholds in migraineurs compared to the control group [70].

Only few studies have explored the habituation of cortical AEPs.

The first one reported "potentiation" of N1-P2 amplitude only at high stimulus intensities in migraineurs, contrasting with physiologic habituation in healthy volunteers [71]. This result was not confirmed in another report [66], probably because of methodological differences.

In a successive study [72], the intensity dependence of auditory N1-P2 and habituation for each stimulation intensities was measured and potentiation was found in migraineurs, greater for high-intensity stimulations than for low-intensity stimulations, as opposed to the habituation or absence of amplitude change for all stimulation intensities in controls.

In addition to the study of habituation, another method of dynamic study of auditory evoked potentials consists of the study of sensory "gating." Gating of sensory input is another characteristic of central processing of incoming information. A typical example of this phenomenon is the suppression of the cortical response to a test stimulus delivered after an identical preceding conditioning stimulus.

The middle-latency P50 component of the auditory evoked cortical potential is very sensitive to gating. Gating of the auditory P50 response was markedly reduced in migraine patients compared to healthy volunteers [73], which was considered an expression of reduced short-term habituation [74].

Another method suitable to assess physiologic CNS responses by means of AEPs is the intensity dependence of AEPs (IDAP), which assesses the amplitude increase of auditory evoked cortical responses with increasing stimulation intensities.

IDAP amplitude was found suddenly increased in migraine between attacks with increasing stimulus intensity [71], reflecting a pronounced intensity dependence of auditory evoked potentials (IDAP), which is likely to reflect reduced central serotonin neurotransmission [75].

The increased IDAP normalizes during the migraine attack [76], as well as during other dynamic changes of CNS excitability.

IDAP abnormalities correlate with personality profiles [77], and some authors interpret this finding with lower serotonergic transmission in migraine, but not in posttraumatic headache [77].

Two independent studies [78, 79] found evidence for a familial effect on IDAP in migraineurs, indicative of a genetic background; however, up to now no direct genetic link has been identified.

These hypotheses are fully confirmed in a recent multicentric study [80]. In this large study, in fact, the intensity dependence of auditory evoked cortical potentials is significantly increased during the interictal phase of migraine [80]. The underlying mechanism of these findings is still under debate and might involve lower preactivation levels of sensory cortices, due to thalamo-cortical dysrhythmia, and low serotonergic tone. Nevertheless, the peculiar abnormalities of both visual and auditory cortical potentials, together, have a high sensitivity and specificity to be considered as an endophenotypic biomarker of migraine.

The results of a previous study by Afra et al. [81], which do not report correlations between PR-VEP and IDAP amplitude-stimulus function slopes in patients with migraine, are partially against these hypothesis.

In conclusion, the studies of basal AEPs in migraine have produced divergent results. However, the dynamic assessment (habituation, gating, and IDAP) widely detects a deficit of habituation or potentiation, with evidence for a genetic-phenotypic correlation.

IDAP is not useful for diagnostic purposes, because of its limited repeatability in pathophysiologic studies [82]. This may be related to the fact that the major part of the IDAP increase in migraine could be due to the AEP habituation deficit at high-intensity stimulations [72].

Recent evidence, however, underlines that, if associated with other neurophysiologic methods, they can become more sensitive and specific in order to distinguish different types of headache [80].

On the other hand, IDAP is certainly suitable in longitudinal (to assess the same subjects at different time points) and pharmacologic studies [83].

7.5 Other Brainstem Reflexes: Nociceptive Flexion Reflex, Corneal Reflex, Jaw-Stretch Reflex, Others

7.5.1 Jaw-Stretch Reflex

Up to now, no study has explored jaw-stretch reflex in migraine.

7.5.2 Nociceptive Flexion Reflex

The stimulation of the sural nerve by means of a pair of surface electrodes, placed on the skin at the retro-malleolar site, evokes muscular response (RIII reflex—nociception flexion reflex) recorded electromyographically from the ipsilateral biceps femoris muscle (capitis brevis). The nociceptive flexion reflex (NFR) is a reliable and objective tool for exploring pain control systems in humans [84]. The threshold and amplitude of the RIII reflex are strictly linked to the threshold and amplitude of the concomitant pain evoked by the electrical stimulus, and the RIII reflex has been reported to be significantly inhibited by the activation of diffuse noxious inhibitory control (DNIC) [84–86].

In the older study assessing NFR [87], Sandrini et al. reported a decrease of RIII reflex threshold in severe and evolutive form of migraine and hypothesized, in this clinical condition, an impairment of the serotoninergic antinociceptive system.

In the same way, with an elegant and more recent study, the same authors [88] assessed, in migraine patients, the effects of heterotopic noxious conditioning stimulation (HNCS), in the form of the cold pressor test (CPT), on the NFR. The major finding of this study is that migraine patients showed no inhibition, but there was facilitation of the RIII reflex during the HNCS. The authors conclude that in migraine there is an impairment of supraspinal pain modulation systems that may contribute to the central sensitization.

Other authors [89] described significant fluctuations in the threshold of the nociceptive flexion reflex between the third week of active estrogen treatment and during the hormone-free interval. These fluctuations are more pronounced in women with migraine compared to non-migraineurs (without statistical significance). This "increased sensitivity," mediated by estrogen withdrawal, was interpreted as the trigger of migraine attacks during the hormone-free interval.

7.5.3 Corneal Reflex

Electrical stimulation by means of a thin cotton thread connected to the cathode of a constant current stimulator, air puff, or direct touch to the cornea elicits a contraction of the orbicularis oculi muscle, defined *corneal reflex* (CR), similar to the blink reflex response. The muscular response is recorded from the orbicularis oculi using an electrode placed on each side of the inferior lid. In contrast to the BR, the CR has no early ipsilateral R1, but only a late bilateral R2 response [90]. The corneal reflex (CR) is a naturally protective brainstem reflex and allows the investigation of peripheral trigeminal nerve structures.

Few studies evaluated the corneal reflex in migraine.

One study [91] detected a reduction in the CR threshold and an increased sensitivity to tactile and painful stimulation in patients with migraine during the interictal phase, more marked on the symptomatic side. These findings were interpreted as an impairment of the afferent pathways and/or changes in excitability of the trigeminal pain pathway in migraine patients leading to cortical and subcortical hyperexcitability of sensory pathways.

Another study [92] reported no differences in baseline response areas under the curve (AUC) and latencies of the R2 components of CR between patients and controls, or any significant differences concerning the headache side and no significant influence of oral triptans. The authors conclude that there is no facilitation of the trigeminal system in the headache-free interval and that there is no effect of sumatriptan on this facilitation.

7.5.4 Others

Isolated studies used other less-validated methods in order to assess brainstem reflexes. In one of these studies, Duncko et al. [93] found that migraine is associated with a higher acoustic startle responsiveness that is already present in children at risk of developing the disorder.

7.6 Conclusions

Large varieties of neurophysiologic tools and different protocols have been used with the aim of studying the function of the brainstem in migraine.

None of the studies of the brainstem reflexes reveal completely repeatable and exhaustive results in terms of normality or alteration of the responses of migraineurs compared to those obtained from non-migraine subjects.

Therefore, none of these neurophysiologic methods have such a high sensitivity and specificity that they can be considered able to definitively differentiate migraine from other forms of primary or secondary headaches.

Results that are much more homogeneous have been obtained using protocols for the study of the habituation and recovery curves to paired shocks of such reflexes.

Since the brainstem plays a crucial role in the pathogenesis of migraine, the habituation and recovery of curves of brainstem reflexes could provide valuable information about the status of the brainstem in such disorder.

Overall, interictally migraineurs with and without aura show a time-dependent amplitude increase of evoked potentials and reflexes to repeated stereotyped stimuli compared to normal subjects. This phenomenon was called "deficient habituation" or "lack of habituation" and was seen only during the interictal period for almost all sensory modalities. In this view, this phenomenon is considered a neurophysiologic biomarker of migraine.

Nevertheless, the habituation is a dynamic phenomenon, as it changes when incoming an attack, during the attack and when episodic migraine evolves to chronic migraine. Chronic migraine is a complication of migraine where sensitization makes its appearance and change profoundly the response pattern to incoming inputs.

The interictal dysexcitability may be of subcortical (thalamo-cortical) origin or correspond to a primary cortical dysfunction (impaired inhibition due to disrupted excitatory glutamatergic neurotransmission), or can represent the result of coexistence of both phenomena and can occur in variable degrees depending on patients and on the migraine phases (time from the previous or the next attack and frequency of migraine) [94].

As a result, neurophysiologic methods have had and continue to have considerable importance in the study of the pathophysiologic mechanisms underlying migraine, in particular of the neurobiologic mechanisms modulating the processing of information at different levels, above all with regard to the cyclical and sudden variations of excitability of the CNS in critical phase.

The incomplete repeatability of the different study methods, anyway, does not exclude that these methods may be useful in longitudinal studies, that is, in the same subjects during ictal and interictal phase or at different timings of the illness natural history.

Finally, the different ways of studying brainstem reflexes represent an interesting tool useful to test a drug's efficacy.

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Chapter 8
Spinal Reflexes in Migraine

Armando Perrotta

8.1 Introduction

Migraine is an episodic, recurrent, genetically determined dysfunction of brain excitability that leads to the activation and sensitization of the trigemino-vascular system (TVS) pain pathways [1]. The TVS is represented by the intracranial vasoactive peptide-containing trigeminal nerve endings and the surrounded pial vessels [2]. TVS activation and the related sensitization of peripheral nociceptors are responsible for the classical migraine throbbing pain, while the subsequent sensitization of the second- and third-order trigemino-vascular neurons in the spinal trigeminal nucleus and thalamus accounts for the development of cephalic and extracephalic cutaneous allodynia, respectively [3]. In addition, both sensory afferents from the head that convoy nociceptive input from the cranial vasculature and dura in the spinal trigeminal nucleus and sensory afferents from cervical dermatomes via cervical ganglion converge in the trigemino-cervical complex (TCC) located in the brainstem [4]. These represent the anatomo-functional substrate accounting for extracephalic/cervical pain sensation during migraine attack.

The central sensitization of the pain pathways at trigeminal as well as at spinal level is characteristically detected in pain disorders and leads to an amplification of the CNS response to painful stimuli. In migraine, an abnormal facilitation of nociceptive reflex responses is widely demonstrated at trigeminal level during the attack and worsens with increasing attack frequency [5]. In migraine the presence of extracephalic cutaneous allodynia during the attack suggests that an altered processing of nociceptive stimuli could be not only detected at trigeminal level but at extracephalic district too [5].

The study of the nociceptive spinal reflex responses contributed to recognize the extracephalic processing of the nociceptive stimuli in migraine during both the

A. Perrotta (✉)
Headache and Pain Clinic, IRCCS Neuromed, Pozzilli, Isernia, Italy

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attack and interictally as well as in episodic and chronic migraine, contributing to clarify the physiopathology of the migraine pain and of its evolution toward a chronic form. The most extensively studied spinal reflex in migraine is the nociceptive withdrawal (NWR) or flexion reflex of the lower limb, which represents an objective measure of the functional activity of the nociceptive system in humans [6]. In particular, in the last decade, the study of the temporal summation threshold (TST) of the NWR gave the chance to study the temporal processing of sensory stimuli at spinal level which play a key role in the integration of the sensory signals in physiological conditions as well as in the central sensitization of the pain pathways at basis of the central pain syndromes.

A less investigated, but also noteworthy, spinal response in migraine is represented by the trigemino-cervical-spinal reflex (TCSR), which permitted to explore the functional activity of the TCC. Finally, as the nociceptive spinal and trigeminal responses are modulated by the supraspinal control of pain systems, the study of the NWR and of the TCSR offered the chance to investigate the role of the supraspinal control of pain systems in migraine pathophysiology.

8.2 The Trigemino-Cervical-Spinal Reflexes

The trigemino-cervical-spinal reflexes (TCSRs) responses are polysynaptic, stereotyped, withdrawal, nocifensive, innate reflex responses generated in the extensor neck and proximal flexor muscles of the upper limbs after the nociceptive stimulation of the supraorbital nerve. Following electrical stimulation of SON, two components are detected: an early cervical response (TCR, onset latency 40.7 ± 5.2 ms) and a spinal response (TSR, onset latency 57.5 ± 4.6). TCSRs are devoted to protecting the head after a nociceptive facial stimulation, so moving away the head from the source of pain. In humans the TCSRs are considered nociceptive in nature as the reflex threshold corresponds to the painful threshold, the area of the reflex response increases in parallel with both the intensity of the stimulation and of the painful sensation, and the responses are inhibited by the conditioned pain modulation (CPM) induced by cold pressor test [7].

From an anatomical point of view, these reflex responses reveal the existence of a trigemino-cervical-spinal complex that functionally connects the trigeminal system with the cervical-spinal motoneurons.

The TCSRs allowed us to study the excitability of the trigemino-cervical-spinal complex as well as the functional activity of the supraspinal control of pain in migraine.

The TCSRs have been evaluated in a group of 43 episodic migraine patients (32 without aura and 11 with typical aura) during the pain-free period. No differences were found in reflex response parameters, including reflex threshold, area of the responses, and latency neither between migraine groups nor between migraineurs and healthy controls. Similarly, the CPM induced by cold pressor test revealed no differences in the reduction of the TCSR response size in migraine groups when

compared to healthy subjects. Interestingly, the study of the recovery cycle of the TCSRs returned a recovery curve of the trigemino-cervical responses significantly faster in migraine patients than in controls, while no significant differences were found in trigemino-spinal response. Taken together, the abnormal recovery cycle of the trigemino-cervical reflex suggests that in migraineurs during the pain-free period, an abnormal hyperexcitability in pain processing involves the extracranial connection of the trigeminal system and includes the cervical level. The described condition of hyperexcitability, not sustained by an abnormal supraspinal control of pain, could represent a factor involved in the susceptibility to develop migraine attacks.

8.3 The Nociceptive Withdrawal Reflex

The nociceptive flexion or withdrawal reflex (NWR) at the lower limb is a nocifensive innate reflex response devoted to protecting the lower limb from injurious or potentially injurious stimulation and represents a reliable measure of spinal nociception. In human experimental setting, the most common technique used to evoke the NWR is stimulation of the sural nerve at lateral malleolus level with recording from the ipsilateral capitis brevis of the biceps femoris muscle. The subject is usually seated in an armchair with knee flexed at 130° and the ankle at 90°. Commonly, the stimulus consisted of a train of five 1-ms electrical pulses delivered at a stimulus frequency of 200 Hz, perceived as unique stimulus of 20 ms. The reflex response consists of a double burst of muscular activity, the non-nociceptive RII (40–60 ms, Aβ-fiber activation) and the nociceptive RIII (80–120 ms, Aδ-fiber activation) response. As for other nociceptive reflex responses, the nociceptive nature of the NWR is sustained by the close relationship between the reflex threshold and the subjective pain threshold, as well as by the positive relationship between the reflex magnitude and pain intensity ratings (see [6], for review). Based on these characteristics, the NWR represents a suitable tool to investigate several aspects of the pain processing at spinal level in physiological and pathological conditions, including migraine.

In the middle of 90 s, the temporal summation of the RIII nociceptive response has been demonstrated when a repeated non-nociceptive electrical stimulation is delivered [8]. The temporal summation of the NWR is represented by a progressive increase in magnitude of the NWR response after a series of constant-intensity electrical stimuli activating Aδ and C fibers [6, 8–10].

In human and animal physiology, the temporal summation of sensory neuronal responses to non-nociceptive or nociceptive stimuli is a form of neural plasticity that shifts the sensory inflow from tactile to nociceptive or amplifies the nociceptive responses. It consists in a temporary change in excitability of the sensory wide dynamic range (WDR) spinal and trigeminal neurons [11], which respond to both subthreshold and threshold C-fiber stimulation in a graded manner, as function of the frequency and the intensity of the stimulation, in a phenomenon known in

animals as wind-up [12]. In humans, the temporary frequency-dependent facilitation of the WDR neuron activity after constant-intensity stimulation of C fibers at ≥0.3 Hz generates and amplifies pain sensation via temporal integration of non-nociceptive and nociceptive neural responses in a phenomenon referred to as temporal summation of pain [9, 13]. The temporal summation of pain develops in parallel with the temporal summation of the NWR of the lower limb. In particular, the temporal summation threshold (TST) of the NWR reflects the shift of the sensory information from tactile to nociceptive, and it is considered an affordable and objective representation of the temporal processing of nociceptive signals into the spinal cord [6, 8, 10, 14, 15] in both physiological and pathological conditions [16–20].

Another interesting feature of the NWR is that the reflex threshold and the TST are modulated by supraspinal control of pain systems via a spinal-bulbo-spinal arch which is part of diffuse noxious inhibitory descending controls (DNICs) of pain, now referred to as conditioned pain modulation (CPM) [21]. The combined study of TST and CPM in humans allowed to objectively measure the activity of the nociceptive system and of the pain modulatory pathways in physiological conditions and in several pain syndromes, including primary headaches such as migraine.

The NWR has been extensively applied to study the physiopathology of the migraine pain by investigating the extracephalic processing of the nociceptive stimuli both during the attack and interictally as well as in episodic and chronic form of migraine.

8.4 Episodic Migraine

In episodic migraine the functional activity of the extracephalic nociceptive system has been studied during the interictal pain-free period and during a migraine attack experimentally induced by the administration of the glyceryl trinitrate (GNT). Episodic migraine subjects during the interictal pain-free period did not show difference in pain processing at extracephalic level by using single painful stimulation at reflex threshold; indeed, no differences in reflex threshold and related subjective pain sensation were found [16, 17, 22]. However, they showed an increased reflex magnitude following a single suprathreshold stimulation (area under the curve at 1.2× reflex threshold), revealing an abnormal facilitation in nociceptive processes [16, 17].

The RIII reflex threshold failed to reveal significant differences in episodic migraine during the interictally pain-free period when compared to control subjects [16, 17, 22]. The RIII area under curve, recorded at 1.2× RIII reflex threshold, was found significantly higher in episodic migraine subjects when compared to healthy subjects who served as controls [16, 17]. The related subjective pain sensation to the RIII area under curve was found higher than in controls, however without reaching the statistical significance.

On the contrary, when the temporal summation of the NWR was measured in episodic migraine subjects during the pain-free interictal period, the TST of the RIII response was found significantly reduced and the related subjective temporal summation of pain significantly enhanced with respect to healthy control subjects [16, 17].

These data suggest an abnormal subclinical facilitation in temporal pain processing at spinal level in subjects with episodic migraine during the interictal phase. A similar subclinical facilitation in pain processing has been detected also using cutaneous stimulation in episodic pain-free migraine subjects [23, 24]. The subclinical facilitation in nociception and pain processing at extracephalic level and during the pain-free period suggests that the pathological mechanisms related to the susceptibility to develop migraine pain are not confined to the trigeminal district but involve the whole body. Based on these evidences, a sort of supraspinal dysfunction in the control of pain can be hypothesized. However, when the functional activity of the supraspinal inhibitory control of pain at extracephalic level was tested by CPM activated by the cold pressor test, subjects with episodic migraine and healthy subjects showed a similar inhibitory pain modulation capability [16, 24].

It is conceivable that migraine patients may have a genetic substrate that predisposes them to a dysfunction of the nociceptive central pathways at both trigeminal and spinal levels. Such chronic subclinical hyperexcitability may contribute to their susceptibility to develop spontaneous migraine attacks. However, the role of supraspinal modulation/inhibition of pain in episodic migraine remains to be elucidated.

The oral administration of GTN induces a migraine-like attack in migraine subjects clinically indistinguishable from a spontaneous one, so representing a well-established experimental model of migraine in humans [25]. When a migraine attack is experimentally induced by the administration of GTN, in migraine subjects, a significant reduction has been observed in TST of the NWR from 60 to 180 min after the NO-donor administration. Interestingly, the facilitation in pain processing, revealed by the reduction of the TST, was detected earlier (from 60 min) than the average onset time of the migraine pain phase and was more evident in migraineurs who developed a migraine attack compared those who did not [17]. Furthermore, the effect of the GTN administration in inducing migraine attacks in migraineurs is earlier and more pronounced the higher the frequency of migraine attacks, regardless the response to the provocative test [26]. These data confirm that migraine subjects are more prone to develop a facilitation in extracephalic nociceptive pathways rather than subjects who do not suffer from migraine and that the exposure to a high number of migraine attacks makes these subjects more prone to develop spinal sensitization and represent a risk factor for migraine progression. This behavior could represent or reveal the pathophysiological substrate at the basis of the shift from an episodic to a chronic form of migraine in such migraineurs rather than in others.

8.5 Chronic Migraine

Chronic migraine is defined by the recurrence of migraine headache for not less than 15 days per month for at least 3 months. Chronic migraine is considered both a huge clinical problem and a pathophysiology challenge. However, it represents an interesting model to study the plastic adaptation of the nociceptive system to a recurrent pain condition.

The study of the NWR in chronic migraine revealed a significant reduction in reflex threshold with a normal ratio between pain threshold and reflex threshold, as well as an inverse relationship between headache severity evaluated by means of the total pain index and RIII threshold values [22]. In subjects with chronic migraine complicated by medication overuse headache, the NWR threshold and the TST of the NWR were significantly reduced, and the AUC at 1.2 times the reflex threshold was significantly increased when compared to both healthy controls and episodic migraine subjects [16]. Furthermore, in parallel with the facilitation of the nociceptive responses, the supraspinal inhibitory control of pain tested by the CPM resulted as defective or less effective in inhibiting the nociceptive responses themselves [16]. Interestingly, the sensitization of the pain pathways and the effectiveness of the supraspinal control of pain were significantly improved after a detoxification treatment from the overused drug [16]. These electrophysiological findings suggested that the progressive facilitation in pain progressing observed in a graded fashion from episodic to chronic migraine could be sustained by an alteration of the central modulatory inhibitory pathways and that the symptomatic medication overuse represents an aggravating but modifiable pathophysiological chronification factor.

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Chapter 9
Sensory Processing and Sensorimotor Integration in Migraine

H. Evren Boran, Hayrunnisa Bolay, H. Andreas R. Gantenbein, and Heiko Pohl

Abbreviations

CM	Chronic migraine
CSD	Cortical spreading depression
GABA	Gamma amino butyric acid
HFO	High-frequency oscillations
ICF	Intracortical facilitation
ISI	Interstimulus interval
LICI	Long-interval intracortical inhibition
LP	Lateral posterior nucleus
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MEP	Motor evoked potential
NDSD	Non-dermatomal sensory deficits
PAS	Paired associative stimulation
PPC	Posterior parietal cortex

H. E. Boran
Department of Neurology and Clinical Neurophysiology, Faculty of Medicine, Gazi University, Ankara, Turkey

H. Bolay (✉)
Department of Neurology and Algology, Faculty of Medicine and Neuropsychiatry Center, Gazi University Hospital, Gazi University, Ankara, Turkey
e-mail: hbolay@gazi.edu.tr

H. A. R. Gantenbein
Department of Neurology and Neurorehabilitation, Reha Clinic, Bad Zurzach, Switzerland
e-mail: a.gantenbein@rehaclinic.ch

H. Pohl
Department of Neurology, University Hospital Zurich, Zurich, Switzerland
e-mail: Heiko.Pohl@usz.ch

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REM	Rapid eye movement
RMT	Resting motor threshold
rTMS	Repetitive TMS
S1	Primary somatosensory cortex
SAI	Short-latency afferent inhibition
SICI	Short-interval intracortical inhibition
SSEP	Somatosensory evoked potential
STD	Somatosensory temporal discrimination
STDT	Somatosensory temporal discrimination threshold
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TRN	Thalamic reticular nucleus
TTH	Tension-type headache
VPL	Ventral posterolateral nucleus
VPM	Ventral posteromedial nucleus
VPN	Ventro-posterior nucleus

9.1 Introduction

Multimodal sensorial disruption is one of the characteristic features of migraine headache attacks. Up to 12 h before and during a migraine attack, patients may experience sensory stimuli (light, sound, and odors) as unpleasant or even painful. Sometimes, migraineurs report these as being triggers of their attacks as well [1, 2]. Photophobia is present in approximately 50–90% of migraineurs and often the intensity of the headache increases with light exposure or certain light patterns [3, 4]. About 25–45% experience osmophobia during attacks and half of them report that strong odors (e.g., perfume, deodorant, coffee, fried dishes, as well as cigarette smoke) may trigger attacks [5, 6].

When allodynia is present, pain may be induced by non-painful stimulation such as mild touch, shaving, dressing, and combing hair. In approximately 65%, this manifests primarily in the periorbital region and spreads to extra-cephalic regions [7, 8].

Photophobia, phonophobia, osmophobia, and allodynia are thought to be clinical correlates of central sensitization. An increased sensitivity to sensory stimuli during the premonitory phase (especially photophobia and phonophobia) is believed to occur independently from trigeminal inputs during an attack [9–12].

In addition, the ability to distinguish two identical somaesthetic stimuli applied to the same or different cutaneous region in short intervals is often impaired during migraine [13–16].

Sensorimotor integration is an anatomical and functional process with motor orders and sensory feedback. Different sensory modalities need to be identified and translated into coding to plan a movement. Sensorimotor integration is mostly associated with the somatosensory cortex, thalamus, posterior parietal cortex, and motor cortex. The sensorimotor cortex is highly dynamic and associated not only with motor learning but also with cognitive events.

Overall, there is evidence that sensory processing may be affected in migraine patients. Much research has been undertaken to elucidate the underlying mechanisms and to study the implications for sensorimotor integration. In this chapter, we will provide an overview of the involved anatomical structures and physiological processes and discuss the current knowledge.

9.2 The Anatomical and Physiological Basis of Sensory Processing and Sensorimotor Integration

Processing of sensory information occurs in the thalamus, the primary sensory cortex, as well as the posterior parietal cortex.

9.2.1 Thalamus

Neurons in the sensory thalamus receive information from the external environment through the medial lemniscus and transfer them to the cerebral cortex. Thalamic neurons and cortico-thalamic feedback neurons ensure a constant communication between the thalamus and cortex in sensory processing [17].

The thalamic nuclei are subdivided into first-order and higher-order relay nuclei. First-order thalamic nuclei transmit sensory inputs to first-order cortical areas such as the primary sensory cortex (S1) [18, 19]. Higher-order thalamic nuclei, on the other hand, primarily receive input from the fifth layer of the cerebral cortex and forward information to higher-order cortical areas [18]. Thereby, the thalamus mediates synchronization of cortico-cortical oscillations [18, 20].

Cortico-thalamic feedback neurons are located in the cortical layer 6 and their axons project on both the thalamus and the cerebral cortex. In addition to sending monosynaptic input to thalamic relay neurons, axons of cortico-thalamic neurons also provide polysynaptic inhibition relayed by local inhibitory neurons and neurons in the thalamic reticular nucleus (TRN). Therefore, the cortico-thalamic activity has both excitatory and inhibitory effects on thalamic function [18].

Furthermore, cortico-thalamic neurons strengthen the sensory signals transmitted from the periphery to the cortex and sharpen the receptive field [21, 22].

Cortico-thalamic feedback affects gain and responsiveness of thalamic neurons at both local and global levels. At the local level, cortico-thalamic feedback selectively increases the sensory response of individual thalamic neurons in somatosensory, auditory, and visual systems [23, 24]. At the global level, cortico-thalamic projections adjust the responsiveness of thalamic neurons during sleep and wakefulness. In addition, cortico-thalamic feedback modulates the sensory responses in the thalamus [25, 26]. More recently, cortico-thalamic feedback was found to increase thalamic response to painful stimulation and to increase the flow of information between the thalamus and somatosensory cortex [27, 28].

The thalamic reticular nucleus (TRN) is a layer of GABAergic neurons surrounding the sensory thalamus. Its neurons project to the thalamus and receive input from both thalamo-cortical neurons and the cortex. Neurons of the TRN are non-reciprocally linked to thalamo-cortical neurons [29, 30]. Multiple brain regions, such as the prefrontal cortex, the amygdala, other thalamic regions, and the basal forebrain region, indirectly affect cortical activation by projections to the TRN [31, 32]. Open-loop connections may be a potential substrate for long-range modulation of cortical activity, and, paradoxically, they are involved in increased thalamo-cortical signal current and signal propagation in the thalamus [33, 34]. Based upon these findings, it is thought that the TRN modulates transmission of information to the cerebral cortex [29, 35, 36]. The TRN controls the response mode of thalamo-cortical neurons, and the flow of sensory information to the cortex, mediates lateral inhibition and maintains the sleep [29, 36, 37].

The thalamo-cortical neurons have two spiking response modes—bursting and tonic activation [37]. Thalamic burst firing plays an important role in sensory gating. It occurs spontaneously in cases of neuropathic pain and noxious stimulation. Inhibition of thalamic burst firing can lead to changes in nociceptive responses [38]. Burst firing occurs during slow-wave sleep as well as sleep spindles [29] and may be associated with relief of migraine pain or migraine attacks during sleep.

Tepe and colleagues showed for the first time that spreading depression waves in the cerebral cortex could invade and activate the TRN in awake rats [39]. While the TRN has seven anatomically distinct sectors of motor, limbic, and sensory processing, cortical spreading depression (CSD) selectively activates the visual sector of TRN. Administration of valproic acid as well as calcitonin gene-related peptide receptor antagonist inhibited CSD-induced activation of the TRN [39, 40]. Dysfunction of the GABAergic neurons in TRN by CSD results in enhanced transmission of sensory information to the cerebral cortex and hyper-responsiveness to sensorial stimulus, as seen in migraine. Given that TRN plays a key role in sleep, selective attention, lateral inhibition, and discrimination of sensory stimuli, studying the complex role of the thalamus in is crucial to understand clinical features and sensory impairment in migraine [41].

Thalamo-cortical somatosensory projections from the ventral posterolateral nucleus (VPL), the ventral posteromedial nucleus (VPM), and the lateral posterior nucleus (LP) reach primary and secondary somatosensory areas. Efferents of the ventro-posterior nucleus (VPN) transmit the sense of touch and pain. Recent paper evaluated the potential participation of thalamocortical network interruption in development of sensory dysfunction accompanying migraine headaches [41].

9.2.2 Sensorimotor Cortex

The posterior medial nucleus of the thalamus transmits somatosensory information to layer 1 of the primary somatosensory cortex (S1), which consists of Brodmann's areas 3a, 3b, 1, and 2 [42–44]. Sensory neurons in S1 project to the primary motor

cortex (M1) both directly and via thalamo-cortical connections [45, 46]. Precentral and postcentral gyri together are termed sensorimotor cortex.

Electrophysiological studies have shown that layer 4 of M1 receives excitatory inputs from the thalamus and sends unidirectional excitatory outputs to layers 2 and 3 [47]. While nearly half of the synapses in M1 are excitatory, synapses in S1 are both excitatory and inhibitory [48]. Feedforward inhibition occurs in layer 1 instead of layer 4 of M1 through thalamo-cortical projections [49].

Direct projections from S1 to M1 and projections from the thalamus to M1 are important for somatosensory motor integration that will be discussed below [50]. In addition, the somatosensory cortex is crucial for motor learning [51–53].

9.2.3 The Posterior Parietal Cortex

Different sensory modalities such as visual, somatosensory, prefrontal, and auditory are integrated in the posterior parietal cortex (PPC). It is connected to somatosensory and motor areas [54, 55], to prefrontal motor areas both directly and through networks [56], and to the M1 via monosynaptic projections [57]. PPC neurons play a role in planning, controlling, and correcting movements. These neurons encode dynamic information about motion [58, 59].

9.3 Somatosensory Processing

9.3.1 Habituation, Sensitization, and Allodynia

Somatosensory evoked potentials (SSEPs) have been used to study processing of somatosensory signals. To that end, the median nerve is stimulated using non-noxious stimuli and an evoked potential—the negative N20-peak—is recorded from the contralateral somatosensory cortex using EEG or magnetoencephalography [60].

The responsiveness of the brain to external stimuli varies. A decrement of responses to repetitive stimuli is referred to as habituation [61]. An increase in responsiveness on the other hand is termed sensitization. The presence of two independent systems (i.e., habituation and sensitization) influencing the reaction of a biological system has firstly been hypothesized by Groves and Thompson in their dual process theory of response habituation [61, 62]. When confronted with a new stimulus, sensitization may occur first; habituation follows later, if sensory stimulation persists.

These phenomena have been studied in migraine patients recording SSEPs. In one study, sensitization was assumed when the average amplitude of the first 100 stimulations was higher than in healthy controls. This was the case in patients suffering from migraine without aura examined during an attack [63]. When two further blocks, each with 100 stimulations were added, a decrement of the average

amplitude per block compared to the amplitude of the first block was observed in healthy controls as well as in patients suffering from an acute migraine attack. These findings suggest that sensitization is present during a migraine attack [63]. In one study, allodynia was experimentally induced in healthy subjects and led to painful sensations and an increase in amplitude of potentials evoked by stimulation of Aβ fibers [64]. It is thus likely that central sensitization during migraine attacks is caused by painful afferents and manifests as allodynia.

While habituation can be observed in healthy subjects, in migraine patients it is present only during an attack [63]. An interictal lack of habituation has been reported for various sensory stimuli [65, 66]. The reason for this is less clear. According to the "ceiling theory," signal intensity must reach a threshold ("ceiling") in order to trigger habituation [67].

In order to investigate further the mechanism of the abnormalities of the SSEPs, some studies focused on high-frequency oscillations (HFO) [68]. These are superimposed on the N20-peak and may be subdivided in early and late bursts. It is believed that generators of the former are thalamo-cortical afferents and of the latter are inhibitory interneurons in the primary sensory cortex (area 3b) [69, 70]. The amplitude of early HFOs was significantly lower in migraineurs in the interictal period and normalized during an attack. No difference in late HFOs was found. A low amplitude of early HFOs had also been found in previous studies when SSEPs were recorded during non-REM sleep.

Given that the amplitude of early HFOs increases after administration of rivastigmine [71] and given that cholinergic systems are relevant for the sleep-wake cycle, it has been hypothesized that these early HFOs were generated by cholinergic reticulo-thalamic pathways [68]. Consequently, an interictal hypofunction of thalamo-cortical excitatory cholinergic afferents was assumed in migraine patients [68]. This finding again might indicate that the pre-activation of sensory cortices was too small to induce habituation.

In patients with chronic migraine, both sensitization and habituation are found in the interictal period, suggesting a permanent ictal-like state [72]. In addition, a correlation between the degree of sensitization and the number of headache days was found. This finding suggests that an increasing sensitization might indeed lead to habituation as predicted by the ceiling theory.

In patients with medication overuse headache, central sensitization is present, while habituation is absent. It has been suggested these patients are in locked a persistent pre-ictal state [63]. These findings are unexpected given the hypothesis that the absence of habituation in migraine patients is due to the low amplitude of the potential. Since that medication overuse is associated with sensitization, an insufficient signal amplitude seems unlikely [63]. Therefore, it has been suggested that the lack of habituation may be the consequence of a cortical hyper-reactivity [73]. The reduced amplitude of evoked potentials and the reduced activity of thalamo-cortical afferents might represent compensatory mechanism mediated by feedback loops [73]. The lack of habituation might not be due to too little input but to a cortical hyper-excitability. Thus, the ceiling theory may be invalid.

Overall, it is likely that the primary sensory cortex is hyper-excitable and the activity of thalamo-cortical afferents is reduced in migraine patients in the interictal

period. During an attack, cortical excitability normalizes (as indicated by the appearance of habituation) and the activity of the thalamo-cortical afferents increases.

9.3.2 *Energy Metabolism*

Despite their name, evoked potentials probably do not represent stimulus-evoked brain events. Rather they document a phase resetting of different cortical rhythms – in particular alpha, mu, and frontal midline theta rhythms [74]. In migraine patients, SSEPs recorded during attacks have a higher amplitude, compared to healthy controls [63], indicating that sensory stimuli lead to a higher degree of phase resetting.

Higher amplitudes of evoked potentials have been linked to a higher energy consumption of sensory processing ([75], Fig. 9.1). This notion is supported by several studies in which the power consumption in the visual cortex was studied using MR spectroscopy before, during, and after stimulation [76–80].

In migraine without aura, lactate levels were normal at all times [77]. However, two studies reported low phosphocreatine, low adenosine triphosphate, and an

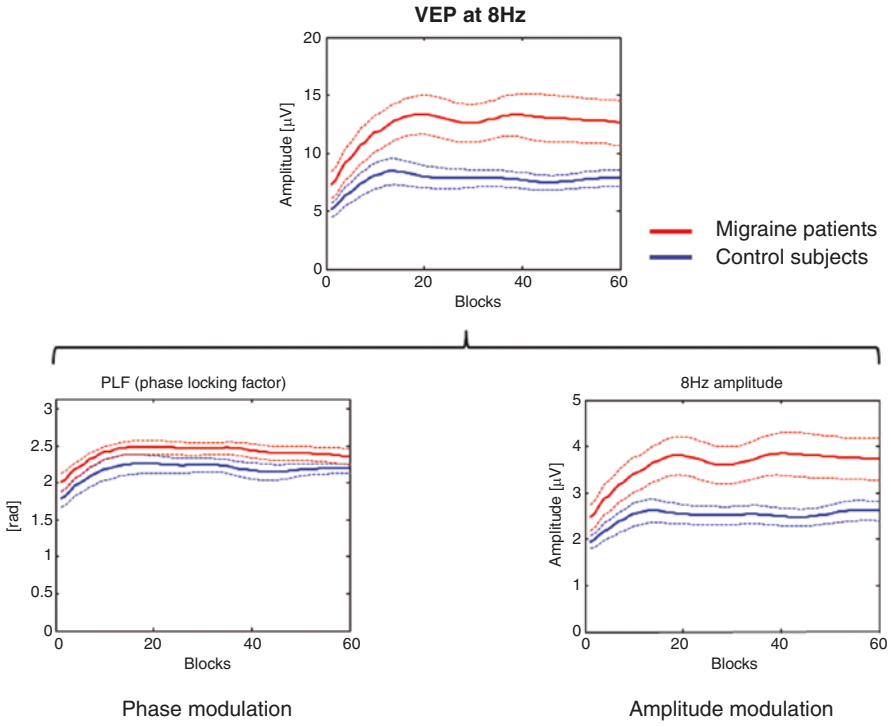

Fig. 9.1 The figure below shows that amplitude differences of visual evoked potentials at 8 Hz stimulation between migraine patients and control subjects are mainly explained by single-sweep amplitude, rather than phase modulation of EEG activity. Amplitude variation is thought to be more energy demanding than phase shift

increased adenosine diphosphate suggesting an altered energy metabolism [78, 79]. In migraine with aura, lactate and adenosine diphosphate levels were high and phosphocreatine was low even in the absence of sensory stimulation [76, 80]. In addition, muscles biopsies revealed an abnormal energy metabolism as well [80].

The precise pathophysiology of the energy metabolism in migraine is yet to be understood. Nevertheless, these findings led to the idea of migraine being due to a defect of the oxidative energy generation [81]. Therefore, it was hypothesized that strengthening the mitochondrial function may help to prevent attacks. Indeed, riboflavin and co-enzyme Q10 reduce the attack frequency in many patients [82–85].

9.3.3 Sensory Gating

Large amounts of sensory information are collected by the nervous system at every instant. While some of these data may be relevant, others are not. The process of selecting important input is referred to as sensory gating. It is studied by measuring the capacity of the brain to filter repetitive stimuli. To this end, two stimuli are commonly applied in close temporal relationship and cortical evoked potentials are registered using electro-encephalography or magnetoencephalography. The so-called gating ratio reflects the amount of attenuation of the second signal. It is calculated by dividing the amplitude of the second signal by the amplitude of the first. Cortical potentials may be evoked using different sensory input, like acoustic, visual, or sensory signals [86].

Two studies examined sensory gating in headache patients [87, 88]. Non-painful electric stimuli were applied to the left index finger and magnetoencephalography was used to record responses from the contralateral primary sensory cortex. The main finding was that the gating ratio was higher in patients with migraine than in controls and higher in chronic migraine than in episodic implying a reduced attenuation of the second stimulus in these groups. There was a positive correlation between the number of headache days and the gating ratio [87, 88].

The mechanisms underlying these findings are unclear. While a true gating deficit may be present (i.e., an incomplete suppression of repetitive stimuli because of a cortical hyper-reactivity), it should also be considered that the small amplitude of the first signal might have been insufficient to induce gating [87].

9.3.4 Somatosensory Temporal Discrimination

The ability to distinguish two identical somaesthetic stimuli applied to the same spot or different cutaneous regions in short intervals is referred to as somatosensory temporal discrimination (STD) [13]. It is crucial for somatosensory

functions such as kinesthesia, graphesthesia, and stereognosis [89, 90]. The somatosensory temporal discrimination threshold (STDT) is defined as the shortest delay between two stimuli that still allows discrimination and differs between body areas [13].

Different studies evaluated STD in migraine patients [14–16]. Boran and colleagues examined the STDTs of the upper extremity (dermatome C7) and face (mandibular nerve) in patients with episodic migraine and healthy volunteers. While no difference could be found interictally, an approximately two- to four-fold prolongation was observed in all regions during an attack [14]. In the contralateral upper extremity and the ipsilateral face, STDTs were significantly longer compared to other regions. These prolongations were thought to have resulted from alterations of central pain perception. However, it has been suggested that a significant prolongation of the contralateral upper extremity and ipsilateral face cannot be explained by the impairment of sensory networks alone [14].

In patients with chronic migraine (CM), STDTs are approximately three times longer than in healthy volunteers—even on days without headache. This finding stands in contrast to episodic migraine where normal interictal STDTs were found. This suggests that the impairment of sensorial processing is sustained in chronic migraine [15]. Again, patients with chronic migraine seem to be locked in an ictal state. In patients with tension-type headache (TTH), on the other hand, STDTs are unaltered [16]. Therefore, STD may be used as a biomarker for chronic migraine as well as to differentiate migraine from TTH [15, 16].

Abnormal STD does not only occur in migraine; it has been linked to cerebral damage in different locations. Lesions in the primary somatosensory cortex, the internal capsule, and the thalamus may cause impairment of both sensory perception and STD. Lesions in the posterior parietal cortex, head of the caudate nucleus, putamen, medial thalamus, and lenticular nucleus do not affect sensory perception but lead to abnormal STD. Finally, a bilateral lesion of the supplementary motor area may be associated with impaired STD as well [91]. In healthy subjects, fMRI imaging revealed the inferior parietal lobule, the middle and inferior frontal gyrus, the anterior part of the right insula, the right anterior cingulate gyrus, as well as the cerebellum to be relevant for STD. The pre-SMA and the anterior cingulate gyrus are thought to be specific for the task [92].

Higher STDTs also occur in patients suffering from movement disorders such as Parkinson's disease, dystonia, and multisystem atrophy [93, 94]. Consequently, basal ganglia are likely to play an important role in temporal discrimination. The affection of STD in Parkinson's disease is thought to be due to an impairment of sensorimotor integration, timing, and projections to the supplementary motor area [95]. Finally, STDTs are higher in patients with cerebellar atrophy [96].

Some of the structures involved in pain perception during migraine attacks such as the insula, cingulate gyrus, cerebellum, and basal ganglia are known to play a role in STD impairment [97]. Thus, changes of STDTs in migraine patients could arise from a transient impairment in these areas [14].

9.3.5 Non-dermatomal Sensory Deficits

About 20–40% of patients suffering from chronic pain complain about sensory deficits ipsilateral to their pain, so-called non-dermatomal sensory deficits (NDSD), and migraine patients are not spared from these constraints [98, 99].

The absence of anatomical lesions in the peripheral and central nervous system often led to speculation about "hysteria" or a conversion disorder [100]. However, careful sensory testing revealed significantly higher thresholds for mechanical and painful stimuli ipsilateral to the pain suggesting functional changes of sensory processing [98].

Imaging studies were undertaken to help understanding these findings. Riederer and co-workers investigated gray matter changes in patients with NDSD [101]. They discovered an increase in gray matter in the right primary sensory cortex, in the thalamus, and bilaterally in lateral temporal regions and the hippocampus. Patients with chronic pain but without NDSD had been included in the study as controls and had changes in similar areas but to a lesser extent. An association with psychiatric disorders was not found. Egloff et al. studied NDSD using FDG-PET imaging and found a significant hypometabolism in the contralateral post-central gyrus, posterior insula, putamen, medial temporal gyrus, cuneus, superior and inferior temporal gyrus, as well as ipsilateral putamen and precuneus [102].

While these findings support the hypothesis of a dysfunction of the central nervous system having caused the symptoms, the precise pathophysiology remains elusive. It has been suggested that NDSD may be the consequence of the central nervous system trying to reduce pain by suppressing sensory afferents [103]. Another hypothesis is based upon the increase in gray matter in and the hypometabolism of the lateral temporal gyrus. Given that dysfunction of this region may be associated with a neglect, a perception disorder might explain the sensory complaints [101]. In the past, the finding of neglect-like symptoms in patients suffering from complex regional pain syndrome had led to the question whether we are "neglecting neglect" [104, 105]. Based upon these findings, one may wonder whether the possibility of an acquired neglect in NDSD should receive greater attention.

9.4 Sensorimotor Integration

Relevant sensory data need to be identified and different sensory qualities be translated into a common coding to plan a movement. This process is referred to as sensorimotor integration.

Much information on executed movements such as muscle contraction and body kinematics converge on the sensorimotor cortex [106–108]. Irrelevant information having been filtered by sensory gating, the remaining data are integrated to plan, monitor, and optimize current and future movements [109]. This complex process is influenced by different factors such as training, motivation, purpose, and neuronal excitability [109].

Some studies tried to evaluate whether altered sensory information may have repercussions in motion planning in migraine patients. To this end, the motor cortex was investigated using transcranial magnetic stimulation (TMS).

Increased excitability was found and suggested that neurophysiological findings have a role in the mechanism of migraine [110, 111]. Increased motor threshold and increased cortical excitability or decreased inhibition in migraine patients was shown [110]. Contradictory results were found in other studies. It is thought that there is dysregulation of cortical excitability in migraine patients whether cortical excitability is decreased or increased. This change in cortical excitability may play a role in explaining the different symptoms in migraine patients.

The amplitude of motor evoked potentials (MEPs) can be measured in peripheral muscles after cortical stimulation is applied using TMS. Low MEP threshold and high MEP amplitude suggest higher cortical excitability [112]. MEP thresholds were found to be normal, increased, or decreased in migraineurs [113].

The resting motor threshold (RMT) reflects the excitability of cortico-motor projections. RMT was assessed in the interictal period and directly after an attack-day in one study. RMT was negatively correlated with the number of days after the migraine attacks in migraine patients [113].

An inhibitory effect is expected in low-frequency repetitive TMS (rTMS) ($\leq$1 Hz), while an excitatory effect is expected in high-frequency rTMS ($\geq$5 Hz) in healthy people [114]. The intracortical facilitation circuit of the motor cortex of migraine patients with aura was significantly activated with 1 Hz rTMS at 90% of the RMT even though it should have been inhibited [115]. Excitatory systems are easily activated in migraine patients with aura at 5 Hz rTMS at 110% and 120% of RMT compared to migraine patients without aura and healthy volunteers. On the other hand, inhibition was observed in migraine patients with 130% of RMT at 5 Hz rTMS, while MEP facilitation was observed in healthy individuals [116]. These paradoxical responses were interpreted as being due to cortical homeostatic metaplasticity. In a hyperactivated cortex, the excitability of the cortex should be maintained in the physiological range when stimulating with low-frequency or high-frequency rTMS [117, 118].

Paired pulse TMS activates inhibiting or facilitating intracortical interneurons, which project to the corticospinal tract. To inhibit the cerebral cortex, short interstimulus interval (ISI) of 1–5 ms (short-interval intracortical inhibition, SICI) and long ISI of 50–400 ms (long-interval intracortical inhibition, LICI) are used. Whereas ISI of 6–30 ms is used to facilitate the cortex (intracortical facilitation, ICF) [119, 120]. Some investigators found increased ICF [121] or decreased SICI [115, 122] supporting the increased hyper-excitability hypothesis in migraine, while others did not. Changing the severity of the test stimulus has a significant effect on cortical inhibition and facilitation in healthy individuals in this paradigm [123, 124]. Test stimulation at 110%, 130%, and 150% of the RMT and 10 ms of ISI for ICF, 2 ms of ISI for SICI, and 100 ms of ISI for LICI was used in another study. Significantly, facilitation was observed by using test stimulation at 110% of the RMT compared to controls in ICF paradigm [125]. ICF is mediated by glutamatergic functions while SICI is mediated by $GABA_A$ receptors and LICI is mediated by

$GABA_B$ receptors. The decrease of postsynaptic activity decreases the threshold for long-term potentiation (LTP) and increases the threshold for long-term depression (LTD). Because of the homeostatic plasticity, cortical neurons adjust the postsynaptic activity level through presynaptic stimulation response, thereby changing cortical excitability [126, 127].

It was shown that cortical excitability is reduced after using anodal transcranial direct current stimulation (tDCS), while cortical excitability is increased using cathodal tDCS [128]. MEP decrease was observed after cathodal tDCS was used in migraine patients with visual aura similar to healthy volunteers, MEP amplitudes returned to baseline at 5th and 15th min by following 5 Hz rTMS. Both groups showed significant facilitation when anodal TDCS was applied. After the 5 Hz rTMS, inhibition was observed at fifth and 15th min in healthy volunteers, while facilitation continued in migraine patients [128]. Inhibitor dysfunction was found to be more prominent in migraine patients with aura than in migraine patients without aura and healthy subjects [129]. Taken together, when evaluating cortical excitability in migraine patients using external modulation, an inhomogeneous group was reported.

Applying stimuli to the periphery and the cortex at different times, inhibition is observed with 10 ms of ISI and facilitation is observed with 25 ms of ISI in the sensorimotor cortex in healthy subjects. This lasts for at least 30–60 min [130, 131] and arises from LTP and LTD.

In one study, long-term synaptic plasticity was investigated. Inhibition of MEP was found to be significantly associated with paired associative stimulation (PAS) 10. While inhibiting, facilitation was observed with PAS 25 in healthy volunteers. However, PAS 10 increased MEP rather than inhibit; PAS25 increased MEP non-significantly in migraine patients without aura.

Short-latency afferent inhibition (SAI) is a modulation of motor response by a sensory stimulus and known to be associated with sensorimotor integration and cognitive functions. SAI is probably related to thalamo-cortical output from cholinergic paramedian thalamic nuclei to M1 or by the direct output from S1 to inhibitory M1 interneurons [132, 133]. A preceding electrical stimulation of a peripheral nerve (conditioning afferent stimulus) transiently suppresses transcranial magnetic stimulation (TMS)-induced motor output. Inhibition of the motor response occurs if the interstimulus interval between the electrical stimulation and TMS is 19 and 50 ms. Thereby, Alaydin and colleagues evaluated the sensorimotor cortex integrity by using SAI paradigm in migraine for the first time [134].

Authors detected a marked decrease in SAI during pre-ictal and ictal periods in migraine without aura patients, which points toward a prominent facilitation to a conditioned stimulus instead of inhibition taking place in the sensorimotor cortex (Fig. 9.2). SAI results in the interictal period in migraine patients were comparable to that of healthy controls. An impairment of the sensorimotor integrity and increased excitability state begins several hours prior to the headache phase in migraine without aura patients. Authors suggested that decreased sensorimotor integration occurs at cortical level and cortical inhibitory volley from S1 to M1 may play an important role in SAI impairment in migraine [134]. This phenomenon could be related to the cortical hyper-responsivity to sensory stimuli and cognitive disturbances

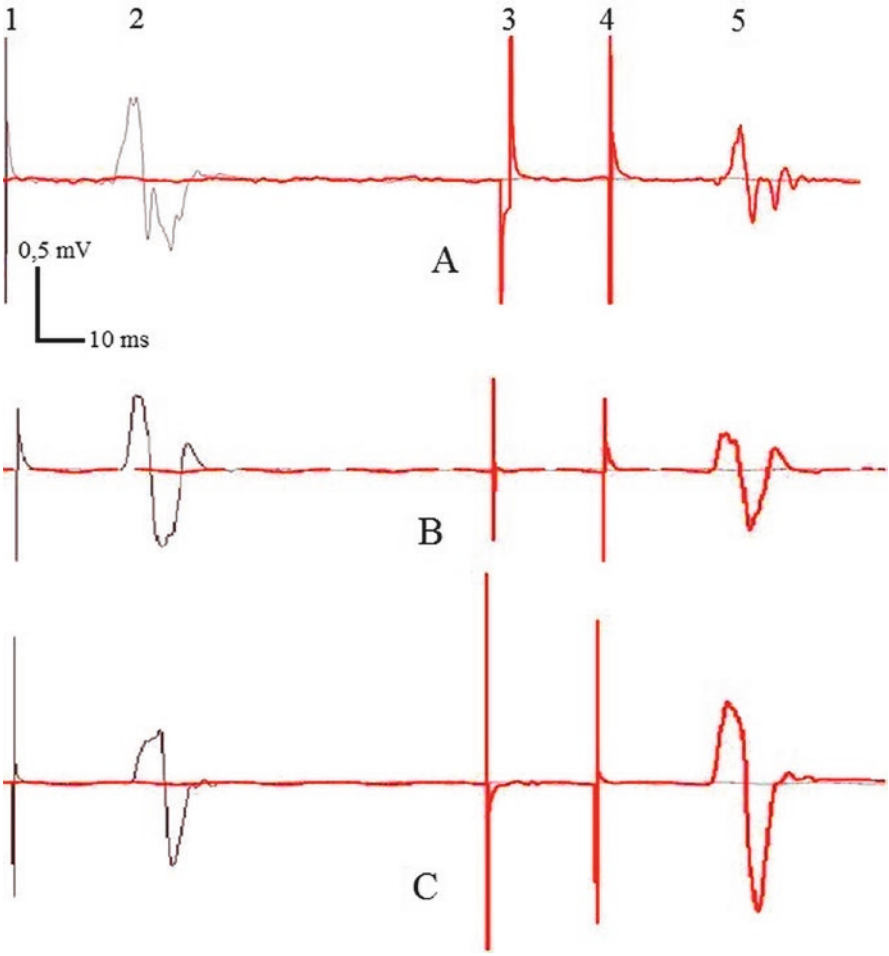

Fig. 9.2 Figure shows typical traces of SAI. MEP amplitudes were reduced with SAI paradigm (5) compared to MEP amplitudes without SAI paradigm (2) in a healthy volunteer (A) and in a migraine patient during interictal period (B). MEP amplitude facilitation was detected instead of inhibition in the sensorimotor cortex during a headache attack in a migraine patient (C). (1) Stimulus artifact of TMS without SAI paradigm. (2) Average of MEP amplitudes before SAI paradigm. (3) Peripheral stimulus artifact in SAI paradigm. (4) Stimulus artifact of TMS in SAI paradigm. (5) Average of MEP amplitudes in SAI paradigm. *MEP* motor evoked potential, *SAI* short-latency afferent inhibition, *TMS* transcranial magnetic stimulation

accompanying migraine attacks because SAI is modulated by cholinergic activity. In support of the latter, a positive effect of a cholinergic drug on SAI was reported [135]. Transient cholinergic dysfunction may play a role in both abnormal sensory processing and cortical excitability in migraine patients. Cholinergic activity of the cortex is also associated with cognitive functions. It is thought that SAI impairment may be related to prodromal and ictal cognitive symptoms [134].

9.5 Conclusions

Sensory processing and sensorimotor integration are affected in migraine patients. Clinically, both allodynia and the prolonged somatosensory temporal discrimination during migraine attacks suggest an impairment of sensory processing. Electrophysiological studies pointed toward a hyper-reactivity of the sensory cortex in migraine. The primary sensory cortex of patients with chronic migraine is sensitized and therefore seems to be fixed in an "ictal state." In addition, the integration of sensory input is impaired as well, because, both before and during a migraine attack, sensory input does not lead to an inhibition of the motor response, but to a facilitation.

Overall, changes of sensory processing and sensorimotor integration in migraine patients probably reflect a cortical hyper-responsivity. The precise pathophysiology, however, remains to be elucidated.

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Chapter 10
Pain-Related Evoked Potentials

Marina de Tommaso, Massimiliano Valeriani, and Mark Oberman

Laser-Evoked Potentials Laser-evoked potentials were introduced more than 40 years ago [1] and now represent the most validated neurophysiological technique for the functional assessment of the nociceptive pathway. Whether galvanic stimuli at painful intensity are used to activate nerve fibers or nervous receptors, both nociceptive and non-nociceptive afferents are stimulated. Since this simultaneous activation raises inhibitory mechanisms at both cortical [2] and spinal [3, 4] level, galvanic stimuli are not suitable to evoke brain responses specifically related to the nociceptive input. As demonstrated by an early microneurographic study, laser pulses applied on the hairy skin stimulate the thin myelinated (Aδ) and the unmyelinated (C) fibers selectively, without a concurrent activation of the non-nociceptive Aβ fibers [5]. The main LEP component is represented by a negative/positive complex (N2/P2), widely distributed over the scalp and reaching its maximal amplitude at the vertex. While the negative component has a mean latency of 200 ms, the positive response peaks at around 350 ms after hand stimulation. The N2/P2 component is preceded by a negative potential (N1) distributed in the temporal region contralateral to the stimulation and a simultaneous positive response (P1) recorded in the frontal region at around 150 ms to hand stimulation [6]. While several cerebral regions contribute to the N2/P2 complex generation, including the middle cingulate gyrus and the bilateral insular cortex, the N1 and P1 components are probably generated by a dipole source in the opercular region [7].

M. de Tommaso (✉)
Applied Neurophysiology and Pain Unit, SMBNOS Department, Bari Aldo Moro University, Bari, Italy
e-mail: marina.detommaso@uniba.it

M. Valeriani
Neurology Division, Pediatric Headaches Center, Bambino Gesù Hospital, Rome, Italy

M. Oberman
Center for Neurology, Asklepios Hospitals Schildautal, Seesen, Germany

Department of Neurology, University of Duisburg-Essen, Essen, Germany

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LEPs are suitable for the study of attentional mechanisms of pain, as the vertex component N2P2 changes in amplitude with relation to distraction [8]. They were thus employed in the study of the complex relationship between motor cortex activation and pain [9, 10]. Different factors of potential attention deviation from painful stimuli seemed to provoke an inhibitory action on the vertex complex [11, 12], indicating an interference effect between contexts of cognitive attraction, arousal, and pain.

Both in PNS and CNS disorders, studies have demonstrated a reduced LEP habituation as a result of an abnormal central pain processing [13, 14]: the loss of habituation likely represents the neurophysiological correlate of the central sensitization, a complex phenomenon comprising spinal and brain maladaptive changes, including phenotypic switch in the expression of spinal neuropeptides, thalamocortical dysrhythmia, and functional reorganization of cortical maps, thus progressively leading to the chronization of pain [15].

In the last years, LEP studies lead to new theory about the pain matrix, largely superimposed to the "salience matrix." In fact, stimuli of the same relevance as the painful ones could recruit the same cortical areas comprised in the LEP generator networks [16]. Reduced habituation seems an important aspect in amplification of pain at central level, as the loss of progressive reduction of painful stimuli relevance and novelty could be a signature of people predisposed to chronic syndromes, whatever being the initial cause of sufferance [17].

10.1 Laser-Evoked Potentials in Migraine

LEP amplitude was normal or even increased in migraine patients, contributing to confirm the anatomical and functional integrity of somatosensory nociceptive pathways [18]. In accord with reduced habituation to multimodal stimuli would be the main neurophysiological pattern in migraine [19]. The dishabituation pattern characterized all LEP components in migraine across different series of stimulation [20] and single responses [21]. Interestingly, this pattern would be intrinsic to migraine, as it was not associated to migraine duration and severity, and it was present just in childhood [13]. Few studies denied the presence of reduced habituation pattern in migraineurs [22], but this apparent contradictory result could be explained by the different mode of habituation phenomenon analysis, or different genetic characteristic of the studied populations [23]. Reduced habituation is present in the inter-critical phase, starts to normalize in the prodromal phase, and resolves during the attack, designing a fluctuating biobehavioral model, where the over-action of the cortical-subcortical circuits goes into restore during the attack phase, according to a homeostatic mechanism [24]. The LEP dishabituation pattern was not reversible in acute phase, its persistence probably subtending the LEP amplitude increase observed during the acute phase [25–27].

More recent studies provided for a new neurophysiological interpretation of LEP habituation phenomena in terms of progressive synchronization and reduction of information flow within the neuronal networks activated by repetitive stimuli [28]. Following painful laser stimulation delivered to the right hand, EEG rhythms exhibited lively information flow, as measured by Granger causality, in migraine patients compared with controls, who went into a progressive synchronization. The rate of information flow was inversely correlated with habituation of averaged laser-evoked responses. This correlation suggested that the phenomenon of progressive adaptation to external conditions could reduce the need for cortical connections between distant regions and create synchronized networks with reduction of stress and energy demand.

Recent studies outlined the role of stimulus-related EEG dynamic in high-frequency—gamma—range to explain complex aspects of migraine. Porcaro et al. [29] observed abnormal thalamic HFO activation under somatosensory stimulation in migraine without aura patients, which correlated with migraine age of onset. The gamma band oscillations (GBOs) evoked by noxious stimuli could be a correlate of subjective feeling of pain [45]. In migraine patients, GBOs evoked by trigeminal and somatic laser stimulation seemed the neurophysiological correlate of pain catastrophizing, anxiety, and depression suggesting a possible utility of the study of high-frequency oscillations to explain clinical characteristics of migraine and possible response to treatments [30].

10.2 Effects of Treatments on LEP Features

LEP amplitude and habituation changed in relation to acute and preventive treatments effects. During migraine attack, the LEP amplitude enhancement concurred with hyperalgesia to painful stimuli. Almotriptan and lysine acetylsalicylate reverted later LEP amplitude increase, in parallel with the effect on migraine intensity [31]. The study confirmed that the resolution of migraine corresponded to the inhibition of the cortical areas generating the P2 wave and subtending the emotive and cognitive compound of pain [26].

Di Clemente et al. [32] described a reversion of reduced habituation pattern of N1 wave after topiramate treatment in migraine without aura. Another study, conducted on patients affected by medication overuse headache [33], reported a normalization of LEP dishabituation after detoxification [34].

In chronic migraine, the therapeutic effect of botulinum toxin on central sensitization is associated with the reversion of reduced habituation of trigeminal evoked responses [35].

The effects of non-invasive neurostimulation on trigeminal nociceptive system were also studied by LEPs. High-frequency TMS of motor cortex reduced LEP amplitude in migraine patients and controls. Migraine patients displayed an evident real and sham effect on hand and trigeminal responses, thus

suggesting the potential utility of this therapeutic approach in the prevention of migraine [36].

Transcutaneous electrical stimulation (TENS), produced with the Cefaly device [37], modulated later LEP originating from the cingulate cortex [38]. Trigeminal TENS could thus act on the cortical regions exerting a pivotal role in pain modulation [17].

Similar results emerged by the use of non-invasive vagal nerve stimulation [39], which reduced later trigeminal LEPs more than the sham device, probably activating the vagal nerve connections with the cortical regions included in the pain/salience matrix [40].

10.3 Pain-Related Evoked Potentials

The recording of pain-related evoked potentials (PREPs) is an objective method for the evaluation of the nociceptive system. It has been developed almost 15 years ago [41] and has proven itself in various clinical and scientific experiments. It is simple, cheap, and non-invasive in its application.

10.4 Electrophysiological Setting

The skin afferents are transcutaneously excited by a concentric electrode (CE). Due to its concentric design and the narrow anode-cathode distance, the CE produces a high current density at low current intensities. Therefore, the depolarization of nociceptive fibers is limited to the superficial layer of the dermis and does not reach the deeper layers that predominantly excite Aβ fibers [41, 42].

The CE, which consists of a metal cathode (D: 0.5 mm) and an anode ring (D: 6 mm), leads to an irritation of nociceptive skin afferents (Fig. 10.1) [41]. The trigeminal stimulation for the elicitation of trigeminal PREPs occurs in the area of the first trigeminal branch with two electrodes placed 10 mm above the supraorbital nerve. The extracranial (somatic) PREPs are caused by nociceptive irritation of the second and third fingers or forefoot of the two phalanges of the second and third toes. The pain threshold is determined by increasing and decreasing stimulus series in 0.01 mA steps. Fifteen to twenty blocks of electrical triples [43] or double pulses [41] are applied (monopolar rectangular pulses; intensity, 1.5 times the individual pain threshold; duration, 0.5 ms; pulse interval, 5 ms; interstimulus interval, 12–18 s) [41, 44]. The PREPs are recorded with a needle electrode placed over Cz and connected to ear electrodes according to the international 10–20 EEG system, which analyzes the negative peak (N1), positive peak (P1), latencies, and N1P1 peak-to-peak amplitudes (PPA) of the PREPs (Fig. 10.1). A strong linear correlation between the PPA of the PREPs and the intensity of pain perception

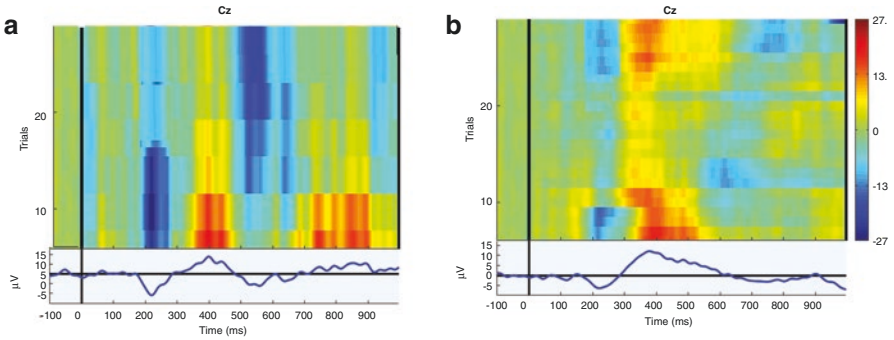

Fig. 10.1 Time course representation of LEP amplitudes by right hand (grand average) across 30 consecutive trials obtained in (**a**) ten normal subjects and (**b**) ten migraine without aura patients. While in normal subjects the N2 and P2 showed a progressive amplitude decrease, migraine patients showed stable or even increased amplitude in the latest trials

(numeric rating scale [NRS]) showed that the PREPs represent a quantitative measure of pain processing [43].

10.5 Activation of Aδ Fibers

After a local treatment with the local anesthetic lidocaine, which led to a loss of the thermoesthesia and pain perception, but not the touch sensation, the PREPs were no longer triggerable up to a certain stimulus intensity [43]. This finding suggests that mainly activated Aδ and C fibers are responsible for the PREPs. In addition, local anesthesia resulted in inhibition of the nociceptive blink reflex response to the extent of 90%. This suggests that only 10% of Aβ fibers contribute to the response after electrical stimulation with CE [43]. The conduction velocity (16–18 m/s) [23] determined after stimulation with the CE and derivation of the PREPs [43] agrees with the conduction velocity of Aδ fibers [44].

10.6 Generators of the PREP

So far, there are no dipole source analyses on the PREPs as in the LEPs, which show that painful electrical stimuli, similar to the painful heat stimuli, activate the operculo-insular cortex in the vicinity of the secondary somatosensory cortex (SII) [45, 46]. Probably the cingulate gyrus is to be regarded as the main generator of the PREPs [45]. The PREPs are vertex potentials. The vertex potentials and thus also the PREPs can be affected by cognitive factors. In one study, Rossi et al. [47] demonstrated by LEPs in diabetic patients that the vertex potential is prolonged in

parallel with the lateralized median latency component (N1), which is likely to be generated by the SII. There is evidence that the sensory-discriminative component of pain is represented by the SII. Since N1 is not severely altered by pain experience or attention and thus provides a reliable indicator of pain transmission [48], the parallel shift of N1 and vertex potentials suggests that pain dysfunction is most likely to be sensory dysfunction in diabetic patients rather than secondary influenced by cognitive factors [49].

10.7 Clinical Applications of PREPs in Headache and Facial Pain

The PREPs may be used in a drug-induced history-making headache to test the efficacy of drug therapies, because it could be shown that the PPA of the PREPs were significantly reduced after the withdrawal treatment for analgesic- and triptan-induced migraine [50]. With additional deduction of the nociceptive blink reflex, the PREPs may also serve to demonstrate central sensitization in headache patients [50]. In addition, the PREPs can also serve the functional diagnosis of symptomatic side dysfunction in trigeminal neuralgia. In combination with the nociceptive blinking reflex, the lesion near the root entry zone of the brainstem could be localized in trigeminal neuralgia [51]. In the future, the PREPs could serve as proof of the effectiveness of therapeutic interventions. An example of this is the fact that the PPA of the PREPs were significantly reduced after cathodal transcranial direct current stimulation (tDCS) and significantly increased after anodal tDCS as an indication for both inhibited and facilitated pain processing [52].

10.8 Comparison of Different Methods of Peripheral Electrical Stimulation

There are numerous methods of peripheral electrical stimulation that cause excitation of Aδ and C fibers and after their excitation can be derived as pain-evoked potentials (Fig. 10.2). Evoked potentials after painful stimuli can be regarded as a special form of somatosensory evoked potentials (SSEP). Inui's needle electrode [53] was able to excite Aδ fibers, while Nilsson's electrode texture and the applied stimulus intensity of the electrode caused predominantly C fibers [54]. A disadvantage of the Inui electrode is its invasiveness. Another electrode design (ten electrodes with a diameter of 200 μm) enabled a spatial summation within the receptive fields of the spinal cord neurons and a high current density at low stimulus intensities in order to promote the activation of Aδ and C fibers [55]. These advantages are also found in the irritation with the CE. Clinical applications of the derivation of

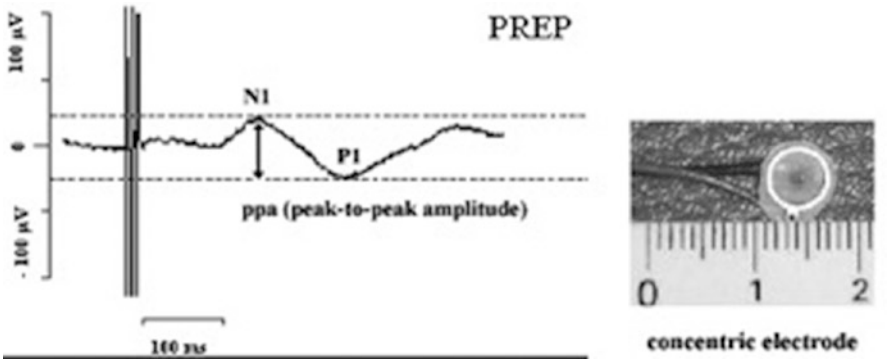

Fig. 10.2 Pain-related evoked potentials obtained by concentric electrode in a healthy subject. The diameter of concentric electrode is reported

pain-evoked potentials are absent in these electrical stimulation electrodes in contrast to the PREPs with the CE.

The skin afferents are transcutaneously excited by a concentric electrode (CE). Due to its concentric design and the narrow anode-cathode distance, the CE produces a high current density at low current intensities. Therefore, the depolarization of nociceptive fibers is limited to the superficial layer of the dermis and does not reach the deeper layers that predominantly excite Aβ fibers [41, 42].

10.9 Conclusion

The PREPs are a simple, inexpensive, and non-invasive diagnostic tool to detect SFN or involvement of small fibers in MFN in routine clinical practice. They can also be used for follow-up diagnostics after therapeutic intervention or proof of central sensitization in headache patients. In addition, they serve to objectify a lesion of the nociceptive pathways. Exact localization diagnostics is so far only incompletely possible with the PREPs. The PREPs probably represent Aδ fiber activity and their generator is located in the cingulate gyrus.

10.10 General Remarks

Both LEPs and PREPs could provide for the study of nociceptive system in headaches and facial pain. They seem reliable in excluding the possible neuropathic origin of the symptoms and in displaying complex mechanisms of altered pain processing, such as reduced habituation or abnormal response to descending modulation, or mechanisms of treatments. While laser-evoked responses are quite expensive and invasive (especially for skin damage by CO2 laser stimulator), they are highly

selective for Aδ and C fibers. The PREPs by concentric electrode could be easily used in clinical setting, but special care should be devoted to the modality of stimulation in order to ensure elective properties for nociceptive afferents [55].

Other methods of nociceptive afferents recording are presently available, so the scenario about the mechanism of pain processing could go into enlargement in primary headaches, thus supporting the physiopathological support of inflammatory peptides such as CGRP and the mode of drug action and disease improving.

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Chapter 11
Pain Perception and Migraine

Martin Uglem

11.1 Migraine Pain

Migraine is a heterogeneous disease with a spectrum of symptoms accompanying the headache pain. The classic migraine headache is characterized by a moderate to severe unilateral throbbing pain. Several other sensory symptoms add to the burden of the headache pain, the most common being nausea and light, sound, and smell hypersensitivity.

Migraineurs may experience symptoms hours to days before the headache attack, as well as symptoms that outlast the headache [1]. Some migraineurs can even predict migraine headaches based on preceding non-headache symptoms. Common prodromal symptoms are tiredness, concentration difficulties, neck stiffness, and increased sensory sensitivity [2, 3]. Migraineurs could report prodromal symptoms several days before the headache started, but analysis showed that the predictive value of these symptoms was rather low until the last 12–24 h before an attack [3].

Allodynia, defined as "pain due to a stimulus that does not normally provoke pain" [4], appears to be an important clinical correlate for altered pain processing in migraine. Allodynia may be assessed by questionnaire, by bedside assessment, or by more detailed experimental quantification as further discussed below. Simple clinical assessment of allodynia may include examination with cotton swab, pinprick, and thermal stimuli, i.e., normally non-painful stimulations [5]. When evaluated by questionnaire, about 50–70% of migraineurs report allodynia during headache, and allodynia is associated with frequency and severity of migraine [6–9]. Seo and Park [10] explored the clinical significance of allodynia compared with photo-, phono-, and osmophobia and

M. Uglem (✉)
Department of Neuromedicine and Movement Science, NTNU - Norwegian University of Science and Technology, Trondheim, Norway

Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway
e-mail: martin.uglem@ntnu.no

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found that both the prevalence of chronic migraine or medication overuse headache, disease duration, and headache intensity were increased in migraineurs with allodynia compared to migraineurs without allodynia, regardless of concomitant hypersensitivity to light, sound, or smell. Accordingly, the presence of allodynia is clearly associated with quality of life and increases the burden of the disease.

A case report showed that, during a migraine attack, allodynia started on the same side of the head as the headache and then spread to the other side of the head and finally to the arm with a progressive increase in magnitude [11]. The authors suggested that this represented activation of peripheral nociceptive neurons, followed by sensitization of second-order spinothalamic neurons and lastly third-order thalamocortical neurons [11]. In one study, at least one of heat, cold, or mechanical ipsilateral trigeminal allodynia was present in 79% of migraineurs 3–4 h into an attack [12]. Only five of those 33 subjects had ipsilateral trigeminal allodynia without contralateral or non-trigeminal allodynia, and two had contralateral but no ipsilateral allodynia [12], thus not providing any clear evidence of sequential activation of first- to second- to third-order trigeminal neurons.

Activation of nociceptive neurons innervating pial, arachnoid, and dural blood vessels and large cerebral arteries and sinuses, combined with a change in central pain modulation, is believed to give rise to the migraine headache [13]. Dysfunction of central nervous system structures involved in modulation of excitability and pain may activate and sensitize the trigeminovascular pain pathway [14–16]. However, the driving force behind this cycling activation is still unknown. Findings from functional imaging studies suggest involvement of hypothalamic, thalamic, and brainstem networks [17–22].

11.2 Experimental Pain

A strictly objective measure of pain perception is not available. Neurophysiological tests can measure *nociception*, the neural process of encoding noxious stimuli [4], but the degree of nociceptive activity does not necessarily comply with subjective pain perception. To quantify pain semi-objectively, a battery of psychophysical neurophysiological tests may be used, commonly defined as quantitative sensory tests (QST). A QST protocol is considered a useful method for psychophysical assessment of sensory detection and pain perception [23]. The protocol may include assessment of detection thresholds, pain thresholds, suprathreshold pain, and pain modulation. Modalities used may be pressure (deep mechanical), tactile (superficial mechanical brush, pins, or filaments), vibration (not used for pain), thermal (heat and cold), electrical (bypassing receptors), visual (light), auditory (sound), and chemical (for the nasal or oral mucosa). Pain thresholds are defined by the external stimulus, e.g., in degrees Celsius for thermal stimuli. An important limitation to the QST is that the tests require cooperation from the subject to define the moment a stimulus is detected, perceived as painful, or to rate the degree of pain experienced in suprathreshold pain experiments.

The thermal part of a QST protocol is particularly helpful in diagnosing small fiber neuropathy, mostly as hypoesthesia and hypoalgesia but also allodynia and hyperalgesia. A pain threshold below the normal range is interpreted as allodynia. Hyperalgesia, defined as "increased pain from a stimulus that normally provokes pain" [4], may be shown by increased pain intensity score to suprathreshold pain stimulation. Both allodynia and hyperalgesia may be due to peripheral sensitization, central sensitization, or both, although by separate and multiple mechanisms [24]. In example, failure of the central pain inhibition system to properly attenuate noxious stimulation may result in hyperalgesia, while failure to inhibit crosstalk between sensory modalities may result in allodynia [25]. More sophisticated QST measures may be applied to assess endogenous pain inhibitory function and endogenous pain facilitatory processes [26]. Conditioned pain modulation utilizes two concurrent noxious stimuli at separate body parts in a "pain inhibits pain" model to measure central pain inhibition. Temporal summation of pain uses repetitive nociceptive stimuli at a frequency of more than three per second to assess pain facilitation. Decreased conditioned pain modulation and increased temporal summation of pain indirectly indicates central sensitization. Thus, different QST findings might provide insights in the underlying pathophysiology.

11.3 Experimental Pain and Migraine

Several studies have investigated responses to experimental pain in migraine. Most of these studies compared responses from migraineurs in the interictal phase and controls, but some also compared responses between migraine phases, migraineurs with or without aura, or episodic and chronic migraine [27, 28].

A recent meta-analysis of QST and migraine identified 109 articles eligible for qualitative analyses [29]. Nahman-Averbuch et al. [29] provided a comprehensive overview of pressure, mechanical, heat, cold, and electrical detection and pain thresholds, as well as suprathreshold pain and pain modulation. The meta-analysis showed lower pressure and heat pain thresholds and higher suprathreshold cold pain ratings in migraineurs compared to controls. Another meta-analysis of pressure pain thresholds over the cranio-cervical region demonstrated comparative results, i.e., lower pressure pain thresholds in migraineurs compared to controls [30]. The studies included in both meta-analyses compared mainly migraineurs in the interictal phase with controls. However, when studies had measurements from multiple migraine phases, the data were collapsed and analyzed as a merged migraine group compared to controls. Thus, the meta-analyses compared migraineurs to controls irrespective of migraine phase, although the findings mainly are representative for the interictal phase. In general, migraineurs seem to be slightly more sensitive to painful stimuli between attacks compared to controls, although the effects are small [27, 28]. Also, some studies have shown increased temporal summation [31, 32] and less efficient conditioned pain modulation [33, 34] in migraineurs in the interictal phase compared to controls, suggesting central

sensitization. No experimental pain test has so far proved reliable in distinguishing between persons with and without migraine. However, a multitude of factors may influence sensitivity in individual patients and contribute to the variation between studies. As discussed below, some of the variations may be explained by cyclical alterations related to proximity to the previous and next attack and some by migraine subtypes.

11.3.1 Pain Perception by Migraine Phase

Only a few longitudinal studies have examined experimental pain sensitivity in the preictal phase (Table 11.1). Neither pain intensity ratings by laser stimulation [35] nor pain scores to painful intranasal ammonia stimulation [19] seem to be

Table 11.1 Pain perception by migraine phase

	Preictal	Ictal	Postictal
Studies showing hypersensitivity			
Longitudinal			
Burstein 2000 [12]		*42* HPT, CPT, MPT	
De Tommaso 2002 [41]		*10* LPI	
Sand 2008 [36]	*11* HPT, CPT		
Moulton 2011 [42]		*8* HPT	
Uglem 2017 [38]	*27* (HPI[a])	*20* CPT, HPI	
Cross-sectional			
Vanagaite 1997 [43]		*19* LPT	
Vingen 1998 [44]		*19* SPT	
Studies without significant alterations			
Longitudinal			
Uglem 2017 [38]	*27* HPT, CPT	*20* HPT	*13* HPT, CPT, HPI
Uglem 2017 [35]	*26* LPI	*19* LPI	*13* LPI
Cross-sectional			
Stankewitz 2011 [19]	*10* API	*13* API	
Stankewitz 2013 [64]		*10* API	
Engstrøm 2013 [37]	*9* HPT, CPT, PPT		*8* HPT, CPT, PPT
Correlations between pain and time to next attack			
Schwedt 2015 [39]	HPT decreased toward the next attack		
Uglem 2017 [38]	HPI increased toward the next attack (no change in HPT or CPT)		

The table shows findings by phase as compared to the interictal phase. The numbers written in italic type represent the number of subjects in the respective phases

API intranasal ammonia pain intensity scores, *CPT* cold pain thresholds, *HPI* heat pain intensity scores, *HPT* heat pain thresholds, *LPI* laser pain intensity scores, *LPT* light-induced pain thresholds, *MPT* mechanical pain thresholds, *PPT* pressure pain thresholds, *SPT* sound-induced pain thresholds

[a]A paradoxical *decrease* in HPI was shown indicating preictal hypoalgesia

altered in the preictal phase compared to the interictal phase. A study by Sand et al. [36] demonstrated decreased heat and cold pain thresholds in the preictal phase compared to the interictal phase. The effect was present when the preictal phase was defined with a 24-h limit, but not with a 72-h limit. Another study that analyzed heat, cold, and pressure pain thresholds with a 48-h preictal limit found no differences [37]. Apparently, different limits may be the source of the discrepant results. However, a follow-up study with a 24-h limit did not reproduce these findings as heat and cold pain thresholds did not change from the interictal to the preictal phase [38]. One explanation might be that preictal recordings were closer to the attack in the study by Sand et al. [36] than in the follow-up study [38], although the latter showed no association between pain thresholds and days to next attack. In contrast, Schwedt et al. [39] found a correlation between heat pain thresholds and time to next attack, as pain thresholds at both the arm and head decreased closer to the attack. Also, pain intensity ratings to suprathreshold heat stimulation have been shown to gradually increase during the interictal period toward the next attack [38]. Thus, studies indicate gradually increasing pain sensitivity in the interictal phase toward the next attack with a more pronounced hyperalgesia during headache.

A study of heat pain intensity scores found an interictal correlation between pain scores and time to next migraine attack and a distinct increase during headache [38]. However, in the 24 h preceding the attack, a subtle decrease of pain scores was present, interpreted as preictal hypoalgesia. These results suggest that significant central events affect processing of pain on the day before headache. Hypothalamic activation has been shown in the preictal phase [17, 18]. Depending on the receptor activated, regions in the hypothalamus may provide either pro- or antinociceptive effects on trigeminal nociception [40]. Thus, it is plausible that preictal hypothalamic activation may cause a transient hypoalgesic effect by increased descending pain modulation. The antinociceptive effect seems to have an effect mainly on suprathreshold pain scores as pain thresholds have been shown to increase or remain unaltered in the preictal phase [36, 38].

Alterations of pain perception are more pronounced in the ictal phase. Studies have shown reduced pain thresholds to either heat, cold, mechanical, visual, and auditory stimulation, increased pain scores to tonic heat, and decreased pain thresholds tested by laser stimulation during attack compared to between attacks (Table 11.1) [12, 38, 41–44]. There are some contradicting findings, but the overall impression is an increased pain sensitivity during headache compared to the interictal phase, which corresponds well with the increase in allodynia and other sensory symptoms during the ictal phase.

Studies of the postictal phase have not shown any differences compared to the interictal phase [35, 37, 38]. When compared to the ictal phase, postictal normalization of cold pain thresholds has been shown [38], indicating a rather fast restoration of pain perception back to interictal levels.

11.3.2 Pain Perception by Migraine Subtypes

Studies comparing experimental pain in migraineurs in the interictal phase and controls have shown variable results, either hypersensitivity or no differences, but never hyposensitivity [27, 28]. Some subgroups may be more hypersensitive than others; for instance, migraineurs with non-sleep-related migraine attacks had lower thermal thresholds than controls [45], while less slow-wave sleep was associated with higher pressure pain thresholds [37].

Subjects with chronic migraine (more days with than without headache) seem to have more allodynia and lower pain thresholds compared to episodic migraineurs, indicating a relationship between altered pain perception and headache frequency [9, 31, 46–49]. However, other studies have neither shown any differences in mechanical or thermal pain thresholds between chronic and episodic migraine [50] nor a relationship between pressure and thermal pain thresholds and migraine frequency [39, 51]. Disease severity may also be of importance, as headache history duration has been shown to modulate cold pain thresholds [36]. As suggested by Peng and May [27], the increased pain sensitivity in chronic migraine may be due to a higher probability of being tested close to the ictal state compared to episodic migraine with longer interictal periods. Other important factors that may increase pain perception in chronic migraine seem to be increased headache severity and level of drug intake [28].

A twin survey suggested that migraine with and without aura are distinct disorders [52]. On the other hand, the International Classification of Headache Disorders, third edition, states that the same person may have both diagnoses [53]. Nevertheless, the few studies that have compared pain thresholds between migraineurs with and without aura have not shown any differences for thermal [36, 38], electrical [32], light [43], or sound pain thresholds [44]. Russo et al. [54] compared heat pain intensity in groups divided by migraineurs without aura and without ictal allodynia, without aura but with ictal allodynia, with aura but without allodynia, and controls. The study showed no differences between the migraine subgroups or compared to controls and no association between pain intensity and migraine severity. Granovsky et al. [55] compared migraineurs with and without aura and found increased temporal summation of mechanical pain stimulation in migraineurs with aura, but no difference in heat and mechanical pain thresholds, or conditioned pain modulation. Perenboom et al. [56] quantified visual allodynia and demonstrated higher scores in migraine with aura compared to without aura and in chronic compared to episodic migraine. Thus, visual stimulation may be better suited to differentiate between migraine with and without aura compared to thermal and pressure pain, although Vanagaite et al. [43] did not find altered visual pain sensitivity in migraine with aura compared to without aura.

Studies of pain thresholds in children with migraine are scarce, but resemble findings shown in adults [28]. Some studies have shown differences in mechanical pain thresholds [57], pressure pain thresholds [58], and laser-evoked pain thresholds [59] compared to controls, but conflicting results exist [60, 61]. A recent study

demonstrated increased heat pain intensity scores in adolescents with migraine compared to controls, but no difference in conditioned pain modulation [62].

11.4 Conclusion

Pain perception alternates within the migraine cycle (Fig. 11.1). Thresholds gradually decrease toward the next attack with a distinct reduction during headache. What happens during the hours to days before the headache starts is still poorly understood. A few longitudinal studies have shown both decreased pain thresholds and paradoxical decreased pain intensity ratings in the preictal phase. The symptoms

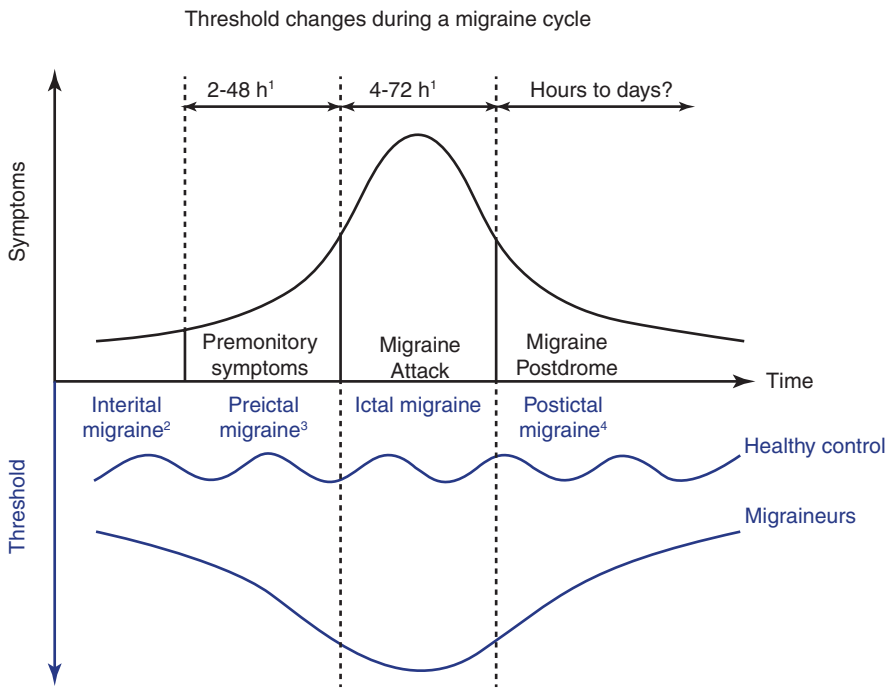

Fig. 11.1 Threshold changes during a migraine cycle. The changes in sensory thresholds over time and their correlation with the clinical symptoms. The undulating threshold in healthy controls reflects the high day-to-day variance as reported in the literature [63]. In this figure, only the phasic changes among migraineurs are depicted; however, the day-to-day variance also stands true to the migraineurs. (1) Definition in the International Classification of Headache Disorders, third edition. (2) No consensus: Certain studies showed lower threshold among migraineurs than healthy controls; others showed no difference. (3) Two studies showed preictal threshold lower than interictal threshold among migraineurs. (4) Hypothetical: No study examined the sensory threshold in the postictal period in comparison with the ictal period (From Peng KP, May A. Migraine understood as a sensory threshold disease. Pain. 2019;160(7):1494–501. doi:https://doi.org/10.1097/j.pain.0000000000001531. Reprinted with permission)

associated with the preictal and ictal phase, in addition to recent functional imaging findings, may suggest thalamocortical alterations by hypothalamic modulation as a generator of the observed preictal hypoalgesia. Findings of cyclical alterations of pain perception support the theory that migraine is a cyclic disorder of the central nervous system related to global alterations of brain excitability and homeostasis.

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Chapter 12
Genetic Basis of the Neurophysiological Findings

Gianluca Coppola, Cherubino Di Lorenzo, and Filippo Maria Santorelli

Abbreviations

ACE	Angiotensin-converting enzyme
CM	Chronic migraine
CNV	Contingent negative variation
FHM	Familial hemiplegic migraine
IDAP	Intensity dependence auditory evoked cortical potentials
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
MTHFR	5,10-Methylenetetrahydrofolate reductase
nBR	Nociception-specific blink reflex
SSEPs	Somatosensory evoked potentials (SSEPs)
TMS	Transcranial magnetic stimulation
VEP	Visual evoked potential

12.1 Introduction

Migraine is an ictal disorder that is characterised by the recurrence of headache attacks accompanied by autonomic symptoms and sensory hypersensitivity. In about 30% of cases, the headache phase is preceded or accompanied by focal neurological symptoms that characterise the migraine aura [1, 2]. Visual symptoms are the most frequent, followed by somatosensory and language symptoms, as well as symptoms attributable to brainstem involvement and motor symptoms [2]. The motor aura is characteristic of a rare form of migraine with aura called familial

G. Coppola (✉) · C. Di Lorenzo
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy
e-mail: gianluca.coppola@uniroma1.it

F. M. Santorelli
Molecular Medicine and Neurodegenerative Diseases, IRCCS – Stella Maris, Pisa, Italy

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hemiplegic migraine (FHM) [3]. FHM can be further complicated by epilepsy. Each year, up to 3% of migraineurs progress to having a chronic daily headache, mainly due to medication overuse [4].

The prevalence of migraine in the general population of industrialised countries varies from 4% to 9% in males and 11% to 25% in females. The prevalence of migraine is lower in Africa and Asia, as well as in African and Asian populations living in industrialised countries, suggesting a race-related genetic susceptibility [5, 6]. The prevalence of migraine also varies with age. In pre-puberty it is present in about 3–5% of children with no difference between the two sexes. Then, the prevalence of migraine progressively increases in both sexes between the ages of 12 and 55 years, after which there is a progressive decline, which explains the low prevalence after the age of 70 years (1– 4%) [7]. However, the increase after puberty is much higher in females than in males, with a ratio of about 2–3:1, depending on the different case studies included. In some cases, the natural history of migraine shows that the clinical manifestations remain unchanged over the years. Contrastingly, they can also significantly change regarding the time course of the attacks and their characteristics, sometimes evolving favourably, whilst in other cases worsening.

The clinical, epidemiological and evolutionary variability of migraines seems to be linked both to acquired environmental factors and to certain genetic factors. For instance, higher baseline headache days, acute medication overuse and depression, which are modifiable and unmodifiable risk factors, are associated with migraine progression [8]. The simultaneous presence of multiple comorbidities can further complicate the clinical and prognostic presentation of migraine. Various disorders can occur as comorbidities with migraine and include neurological, psychiatric, cardio- and cerebrovascular, gastrointestinal and immunological conditions. Each of these has its own genetic load and shares some common characteristics with migraine. For these reasons, some researchers believe that there may be a common genetic background that predisposes some people to migraines and other comorbidities [9].

Overall, its considerable clinical variability, relationship with age and sex, progression and relationship to comorbidities elude to migraine being a polyfactorial disorder that may be based on polygenic pathophysiology. Furthermore, it is well known that migraine runs in multiple members of the same family [10]. However, the genetic basis for this remains unclear.

12.2 Link Between the Genetic Load and Nervous System Dysfunction

The polygenic load in migraine can be seen as the determinant of a genetic vulnerability, modulated by multiple endogenous and exogenous factors, such as physical/mental strain, intense light/noise/odours, stress, diet, sleep and acute medication overuse [11]. This suggests that genetic determinants are responsible for the transmission of a predisposition to an increased risk of suffering from a disorder. The

genetic transmission of this risk would result in the presence of abnormalities called biomarkers of vulnerability. The presence of this trait vulnerability does not imply an immediate manifestation of the disease. Migraine is thought to be associated with the presence of vulnerability biomarkers, including electrophysiological markers that could be inherited by a similar multifactorial genetic background. Early evidence of common neurophysiological patterns in multiple members of the same family with a history of migraine was already highlighted in the pre-molecular era [12] and confirmed in more recent studies based on evoked potentials (EPs) and brainstem reflexes. The most frequently detected electrophysiological abnormality in migraine patients is the 'habituation deficit'. This occurs during the pain-free period in response to any sensory stimulus except the olfactory one. All these abnormalities normalise during a migraine attack [13–22]. Cortical responses to painful stimuli, such as laser stimuli, behave differently as they do not become habituated even during the ictal phase, probably because sensitisation mechanisms come into play.

Coherently with the vulnerability model [11], most of these abnormalities develop early in life and would be found in relatives, including those apparently free of migraine pathology.

Between the pre- and post-pubertal age, migraine patients and healthy controls had similar amplitude and habituation at the recording of contingent negative potentials (CNV). This slow cortical potential can be recorded from the scalp in a contingency condition [23]. After that period, when the brain begins to mature and requires more information to be processed, the CNV amplitude increases and the habituation deficit begins to appear in people with migraines, as compared with healthy controls [23]. The same was not found to happen when researchers investigated visual evoked potential (VEP) amplitude and habituation, because both migraineurs and controls did not habituate to the stimulus repetition. Nonetheless, they found a shortened N180 latency from pre- to post-pubertal age in controls but not in the migraineurs [24].

VEP habituation during stimulus repetition and strong intensity dependence during stimulus increase (IDAP) are abnormal both in parents and in their children. Moreover, children tend to have more abnormal values than their parents, both for visual and auditory evoked potentials and in earlier onset of the disease. This finding led the authors to suggest that impaired cortical information processing is present early in the disease course [25]. In other studies, the CNV amplitude and habituation showed a significant correlation between children that suffer from migraines and their affected parents [26], whilst the IDAP increase showed only a tendency towards the same significant correlation [27]. This interrelation was not observed between children with migraines and their healthy parents, or between healthy children and their healthy parents [26, 27]. This confirms that genetic susceptibility can explain part of the variance of electrophysiological response in migraines.

In a multichannel somatosensory evoked potential (SSEP) study, the age of onset of the disease was positively correlated with the power activity of the right brainstem and thalamus, i.e. the earlier the onset, the more pronounced the neurophysiological dysfunctions [28]. By recording VEPs, some authors have found that a

first-degree relative suffering from migraine shows the same significant deficit of habituation and a similar reduction of first block amplitude of migraine without aura patients, compared to controls [29].

As expected from the vulnerability model [11], individuals with a positive family history of migraine, usually defined as 'high-risk', will generally demonstrate the same neurophysiological abnormalities as migraineurs compared to individuals without a family history of the disorder. Siniatchkin et al. found that high-risk subjects and full-blown migraineurs differed significantly from low-risk individuals since the first two groups shared the same increased CNV and lack of habituation [30]. Individuals with a positive family history of migraine were also studied by recording the nociception-specific blink reflex (nBR), reflecting the activity of the trigeminal system area-under-the-curve and habituation. The cortical potentials were found to be reduced interictally in patients with migraines [21, 31]. Di Clemente et al. found that the first block response area was more reduced in people with migraines and high-risk subjects as compared to healthy controls. Moreover, nBR habituation was nonetheless significantly different between groups, since patients with migraines showed a lack of habituation and that subjects were at high risk of potentiation when compared with the habituation curve of healthy controls [32].

Overall, these results suggest that inheritable factors contribute to the typical interictal abnormal sensory information processing at the trigeminal and cortical level seen in migraineurs.

12.3 Monogenic Forms of Migraine and Neurophysiological Responses

The association of one or more neurophysiological abnormalities with one or more genes may explain a person's vulnerability to one or more aspects of the migraine disorder.

Familial hemiplegic migraine (FHM), a rare dominant inherited form of migraine with aura, is an example of a monogenic subtype of migraine which was considered for a long time a model for the common forms of the disease, especially because, except for the motor symptoms, it presents with the same headache and aura features [3]. To date, three genes have been found to underlie dominant inherited forms of FHM [33–35]: voltage-dependent calcium channel, alpha 1A subunit (*CACNA1A*) for FHM1; ATPase Na+/K+ pump, alpha 2 subunit (*ATP1A2*) for FHM2; and voltage-gated sodium channel, type 1 alpha subunit (*SCN1A*) for FHM3. In recent years, the whole genome/whole exome was used to identify additional causal genes in those patients in which no mutation in one of the three genes had been found. Surprisingly, this has not led to undisputed additional genes. All the FHM genes are involved in glutamatergic neurotransmission and cortical excitability. Therefore, their mutations impair these functions, making the brain more susceptible to cortical spreading depression (CSD), the neurophysiologic phenomenon at the base of

migraine aura [10]. Although patients with FHM and those with migraine with aura share many similarities, a more precise genetic link with the common forms of migraine with and without aura has not yet emerged [36–42]. However, one study that examined whether the mutated FHM genes were associated with the same neurophysiological abnormalities found them in the most prevalent forms of episodic migraine. In patients with FHM, non-specific electroencephalographic abnormalities have often been described both during the attacks (unilateral or bilateral delta EEG activity with reduction of alpha [43–52]) and in the interictal phase (theta abnormalities [46, 53]). Some authors measured VEP habituation, IDAP and nBR in a group of genotyped FHM1 and FHM2 patients. They detected more pronounced VEP and nBR habituation in FHM patients than healthy controls, with no significant differences in IDAP parameters [54]. The limitations of this study are the low number of patients and the use of portable equipment. Nonetheless, these results stand in contrast with those obtained in the most prevalent forms of migraine and contradict the assumption that they share the same pathophysiological mechanisms.

This discrepancy between the neurophysiological results obtained from the monogenic forms of migraine and those of common migraine with and without aura was further confirmed using other neurophysiological methods. In a transcranial magnetic stimulation (TMS) study, a group of ten patients with FHM showed higher resting motor threshold, longer central conduction time and lower MEP amplitude on the ictal paretic side than on the non-affected side. In contrast, MEP amplitudes were significantly increased in a group of patients with common migraine with aura [55].

The FHM1 gene is involved in neuromuscular transmission, and researchers have tried to find neuromuscular fingerprints of genetic abnormalities related to P/Q Ca2+ channels in a broad spectrum of patients with migraine aura. Using single-fibre electromyographic (EMG) recordings, they found subclinical abnormalities in a subgroup of patients suffering from the most prevalent forms of migraine with aura [56–58], whilst the EMG results of FHM patients did not differ from those of healthy controls [59].

The TWIK-related spinal cord K+ (TRESK) channel encoded by the *KCNK18* gene is expressed in all primary afferent neurons in trigeminal ganglia and dorsal root ganglia [60], and it is apparently linked to intrafamilial transmission of migraine with aura [61]. Despite the clear interest of this gene in the pathophysiology of migraine pain, to date, there are no neurophysiological data in humans.

12.4 Association Studies Between Genetic Polymorphisms and Neurophysiological Responses

Several single-nucleotide polymorphisms have been found to be more prevalent in the most typical forms of migraine than in controls. Except for 5,10-methylenetetrahydrofolate reductase (MTHFR), an enzyme in folate metabolism, the vast

majority of reported genetic associations with candidate migraine genes have not been convincingly replicated [62]. Few studies have analysed genotype/neurophysiological phenotype correlations in migraineurs (Table 12.1).

Magis et al. searched for a possible correlation between the interictal features of VEPs and the MTHFR C677T polymorphism in people with migraines [63]. The presence of the 677T allele is significantly associated with a lower N1-P1 VEP amplitude both for the grand average of 600 responses and for each of the six blocks of 100 averages. In the CC subgroup and to a lesser extent the CT subgroup, there was a lack of N1-P1 VEP habituation compared to that found in healthy controls. They interpreted these results as due to a mild neurotoxic effect of homocysteine [63]. Similar VEP results were obtained by another group of researchers [64]. In another neurophysiological study, patients with migraine carrying MTHFR C677TT polymorphism exhibited significantly reduced CNV habituation, in respect to both C677TC and C677CC carriers, and the habituation index values correlated positively with the homocysteine levels with no difference in the frequency of the attacks and MRI findings [65].

Other polymorphisms concerning a variety of genes coding for proteins involved in neurotransmission, vascular pathways, inflammation, metal/ion homoeostasis or glucose metabolism have been involved in migraine [10].

According to the definition of central sensitisation (i.e. increased responsiveness not only to noxious but also to innocuous, peripheral stimuli), signs of sensitisation have also been reported in non-painful SSEP studies, in which cortical amplitudes recorded interictally were larger in patients experiencing CM or medication overuse headache (MOH) than in episodic migraines between attacks [17, 19]. In MOH, the initially higher SSEP amplitudes lacked habituation in subsequent block averages, i.e. further increase, resulting in a 'persistent' cortical sensitisation [17].

These abnormalities in cortical responses to somatosensory stimulation appear to be strongly influenced by genetic factors [66]. Angiotensin II, the product of the cleaving activity of the angiotensin-converting enzyme (ACE), functions as a neurotransmitter. The ACE D/D genotype appears to serve as an influencing factor in migraine attack frequency [67], as well as in substance abuse behaviour [68, 69]. Di Lorenzo et al. [66] sought to verify whether the ACE polymorphism could affect neural plasticity, as assessed by SSEP recording, and the clinical features of MOH. They observed that D/D homozygote carriers, with their elevated levels of angiotensin activation, differed from the D/I and I/I carriers in their response to repeated stimulation and to the type of drugs they overused. D/D carriers exhibited the highest averaged SSEP amplitudes (i.e. reflecting sensitisation) and the most severe deficits in habituation, although other MOH patients did not habituate either. This abnormal neurophysiological pattern gradually disappeared in the D/I and I/I carriers, in whom the cortical response normally habituated [66].

The central sensitisation seems to be strongly dependent on glutamate. Therefore, genes that are involved in glutamate signalling may be implicated in migraines [70]. In a preliminary study presented only in abstract form, the *rs3761555* single-nucleotide polymorphism in glutamate receptor ionotropic AMPA 3 (*GRIA3*) influenced SSEP amplitude sensitisation in patients with MOH [71].

Table 12.1 All neurophysiological findings on the genotype/electrophysiological phenotype correlation in migraine

Authors	Subjects	Polymorphism	Methodology	Outcome's variables	Results
Magis et al. [1]	24 MO 28 MA	MTHFR (C677T)	VEP	Amplitude and habituation	Presence of the 677T allele associated with a lower N1-P1 VEP amplitude both for the grand average of 600 responses and for each of the six blocks of 100 averagings. Lack of N1-P1 VEP habituation in the CC subgroup and to a lesser extent in CT subgroup
Azimova et al. [2]	64 MO 19 MA	MTHFR (C677T)	VEP	Amplitude and habituation	Presence of the 677T allele associated with decreased N1-P1 amplitudes and a lack of habituation
de Tommaso et al. [3]	90 MO 15 MA 97 HC	MTHFR (C677T)	CNV	Habituation	Patients with homozygosis (TT) showed significant decrease of CNV habituation which correlates with the homocysteine levels. In patients, the presence of subclinical brain lesions at the MRI was not related with C677T homozygosis
Di Lorenzo et al. [4]	43 MOH	ACE (rs4646994)	SSEP	Amplitude and habituation	Compared with patients carrying II polymorphism, DD carriers showed more pronounced lack of habituation, with those carrying DI falling in between. In DD carriers, the degree of lack of habituation correlated with the duration of overuse phase. Especially in DD carriers, early amplitude responses increased with the type of acute medication
Di Lorenzo et al. [5]	60 MOH	GRIA3 (rs3761555)	SSEP	Amplitude and habituation	TT carriers showed higher amplitudes compared with those of CC carriers, with CT carriers falling in between

MO migraine without aura, *MA* migraine with aura, *MTHFR* 5,10-methylenetetrahydrofolate reductase, *ACE* angiotensin-converting enzyme, *VEP* visual evoked potential, *CNV* contingent negative variation, *SSEP* somatosensory evoked potential

If we regard habituation loss as an endophenotypic characteristic of migraine, it is worth noting that some genetic polymorphisms involved in neural plasticity could modulate behavioural responses in healthy subjects. Both the brain-derived neurotrophic factor (BDNF) Val66Met and the monoamine oxidase type A upstream variable number tandem repeat (MAOA-uVNTR) polymorphism have been associated with the deficit of habituation at pain-related evoked potential elicited by repeated trigeminal painful electrical stimulation [72, 73]. Considering the well-known involvement of the trigeminovascular system in migraines, a similar study focussing on migraines would be worthwhile.

The neurophysiological abnormalities found between attacks are the simplified expression of simple genetic variants, i.e. they are ideally linked to the additive effect of single-gene polymorphisms [74].

12.5 Conclusions

The vulnerability model, commonly used to explain the emergence of psychopathologies such as schizophrenia, major depression and anxiety, postulates that genetic determining factors are responsible for the transmission of a predisposing vulnerability to a higher risk of suffering from a disorder. The genetic transmission of this risk would result in the presence of abnormalities called markers of vulnerability. It does not imply the immediate overt manifestation of the disorder because it depends on the possible co-existence of genetic and environmental factors [11]. Hence, the vulnerability model incorporates the environmental and genetic origin of the disorder and their interaction. With this model of the emergence of a disease as a basis, the search for new tools to dissect the complex phenotypes of functional disorders has revealed the concept of endophenotypes [75]. It has been found that endophenotypic abnormalities that are not clinically apparent but impact on the phenotypes are the simplified expression of genetic variants, i.e. ideally linked to the polymorphism of a single gene. A functional disorder would thus be constituted by the assembly of different simplified phenotypes and simple genetic variations. Beyond the schemes, endophenotypic markers are complex phenotypes that can be influenced by environmental factors. These complex phenotypes may interact with each other and this could be the cause of the disease worsening or improving.

According to the studies revised in this chapter, the vulnerability model can be easily applied to migraine pathology (see Fig. 12.1).

Some authors have proposed the presence of abnormal information processing of sensory stimuli, i.e. the lack of sensory habituation, as a possible marker of vulnerability. This proposed intermediate phenotype was linked to the polymorphism of single genes, such as MTHFR and ACE. In migraines, the neurophysiological endophenotypic marker can interact with several environmental factors, such as sunlight irradiance [76], stress [77], colour lens [78], the number and the type of acute medication intake [17] and

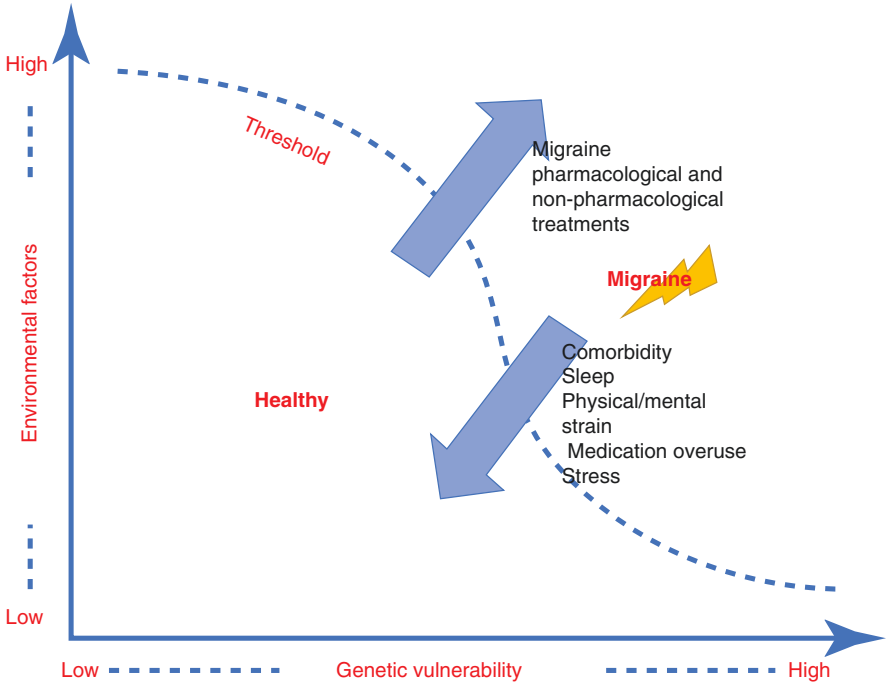

Fig. 12.1 The vulnerability model applied to migraine pathology posits that individuals possess a genetic vulnerability to a migraine that can withstand a certain amount of internal/external stressors due to genes and other biological risk factors and can cope with a certain amount of fluctuations of cortical responsivity. However, once the vulnerability threshold is surpassed, these people may have a higher risk of developing migraines. Comorbidities and other influencing factors lower the migraine threshold by increasing the level of cortical responsivity. Therefore, this may result in the person having a greater susceptibility for migraines. On the other hand, migraine pharmacological and non-pharmacological interventions may increase the vulnerability threshold, preventing the recurrence of migraines (Modified from [11])

migraine preventives [79, 80]. The presence of interictal neurophysiological abnormalities, such as habituation deficit [81], inhibition [82] and thalamocortical activation [83] deficit, has been found to significantly correlate with spontaneous clinical fluctuations in migraine, further confirming this conceptual model.

Therefore, the lack of sensory habituation could be considered a neurophysiological endophenotypic trait associated with the expression of genetic factors that make an individual vulnerable to migraines. This abnormality was found in relatives, including those apparently free of migraine, and thus can be considered a susceptibility marker of possibility.

More studies are needed to verify if this neurophysiological endophenotypic marker is present before the onset of the disease, if it is associated with the disease in the general population and if it can be found in non-affected family members at a higher frequency than that reported in the general population.

It is also of uttermost importance to collect more data on the complex geno- phenotype correlations of clinical and neurophysiological features amongst the different migraine forms. This may help to explain the evolutionary process from episodic to chronic migraine, a debilitating condition in which various polymorphisms have been linked to the disease, its psychiatric comorbidities and dependence behaviour [84–90].

Another possible approach to study migraine vulnerability and its endophenotypic markers is that of epigenetic [91], i.e. verifying whether gene expression patterns change along with a patient's clinic-neurophysiological state.

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Chapter 13
Neuromodulation for Evaluating the Pathophysiology of Migraine

Gianluca Coppola and Andrea Antal

Abbreviations

ISI	Interstimulus interval
MEP	Motor evoked potential
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
PAS	Paired associative stimulation
PT	Phosphene threshold
RMT	Resting motor threshold
rTMS	repetitive Transcranial magnetic stimulation
SAI	Short-latency afferent inhibition
SIFI	Sound-induced flash illusions
SSEP	Somatosensory evoked potential
tDCS	Transcranial direct current stimulation
VEP	Visual evoked potential

13.1 Introduction

Nowadays, thanks to the enormous technical and methodological developments first in neurophysiology and later in neuroimaging, it is proven that the development of symptoms of neurological and psychiatric diseases is more related to the malfunction(s) of brain networks than of focal brain areas. In fact, our brain collects

G. Coppola
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy
e-mail: gianluca.coppola@uniroma1.it

A. Antal (✉)
Department of Clinical Neurophysiology, University Medical Center Göttingen, Georg August University of Göttingen, Göttingen, Germany
e-mail: aantal@gwdg.de

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all of the information from the world (vision, touch, hearing, etc.), at parallel by the peripheral organs. All the information are sent through preferential neuronal pathways to numerous and dispersed brain areas not only directly responsible for processing that specific information but able to process and respond to multisensory stimulation, in order to form conscious perception and memory and induce or modulate learning and cognitive responses [1].

One way to shed light on the causal operations of these networks is to modulate, in an inhibitory or excitatory direction, an area that is part of the network and examine the effect of modulation. This process is commonly called neuromodulation. The two most frequently used techniques for the modulation of the brain's activity are repetitive transcranial magnetic stimulation (rTMS) [2] and transcranial direct current stimulation (tDCS) [3]. At the neuronal level, the mechanisms are based on the application or induction of an electric field in the brain tissue that modifies the passage of ionic currents within the tissue, resulting in changes in the membrane potentials of the neurons and modulate their firings rate. Different neurons, inhibitory or excitatory, can be targeted by these techniques simply by changing the stimulus parameters, including the type, intensity, and duration of the stimulation [4]. Due to their flexible application window, both rTMS and tDCS have been widely investigated as potential non-pharmacological treatment options for various psychiatric and neurological disorders, including migraine [5].

In this chapter we have reviewed studies using neuromodulation techniques to investigate the pathophysiological mechanisms of migraine, including both episodic and chronic types.

13.2 Neuromodulation of the Visual Cortex in Migraine

One of the most frequently detected electrophysiological abnormalities in the migraine brain is a lack of habituation to repeated and stereotyped sensory stimulation [6], including the visual modality [7]. Bohotin and colleagues [8] found that in episodic migraineurs between attacks, 10 Hz rTMS, which is thought to be an excitatory stimulation, applied to the occipital region increased the amplitude of early VEP responses and produces a delayed, but normal, habituation. One Hz rTMS had no significant effect on the altered habituation. In contrast, in healthy subjects, low-frequency stimulation produced a neurophysiological pattern of VEP habituation deficit, such as that of migraineurs, while high-frequency stimulation had no effect. The authors concluded that, since only excitatory stimulation is able to normalize the visual responses of migraineurs, their brain during the interictal period is basically hypoexcitable [8]. In agreement with this hypothesis, several research groups reported that VEP habituation was normalized and phosphene thresholds (PTs) decreased immediately after anodal tDCS over the occipital area in migraineurs [9].

Other researchers showed that anodal tDCS of the left temporal pole, but not sham, normalized VEP but not SSEP habituation in patients with migraine without aura, between attacks [10].

Fumal et al. [11] investigated the cumulative effect of multiple daily rTMS sessions on VEPs. They observed that five consecutive daily sessions of 1 Hz rTMS applied to the visual area of healthy subjects induced an effect on VEPs that lasts for several weeks. In contrast, in migraineurs, the effect of daily sessions of excitatory rTMS lasted for up to 1 week. This short-lasting effect in patients suggests that in migraineurs there is a general deficiency of inducing long-term potentiation and depression-like effects (LTP and LTD) that are thought to be related to the basic neuronal mechanisms of the stimulation. Indeed, when Brighina and colleagues [12] tried to induce a long-term change in visual cortex excitability in migraineurs with aura, they obtained paradoxical effects. Low-frequency rTMS applied to the visual cortex was able to induce an increase in the threshold for eliciting phosphenes in healthy subjects. In contrast, in patients with migraine with aura, the same neuromodulatory procedure induced a decrease in the threshold. These paradoxical effects in response to inhibitory neuromodulation can be interpreted as an expression of a deficit in the mechanisms governing LTD in migraine.

In a blinded case-control study in which high-frequency rTMS was used with the intention to modulate habituation, migraineurs assessed interictally and preictally responded differently from healthy controls. Using large checks as visual stimuli that preferentially activate the magnocellular visual pathway, rTMS reduced N1-P1 VEP habituation in migraineurs in the interictal phase compared to controls. Using small checks that preferentially trigger the parvocellular visual pathway, rTMS reduced habituation in the pre-ictal phase, while it increased or had little effect on habituation in migraineurs in the interictal phase and in controls [13].

That the mechanisms that control LTD are deficient in migraine is further proven by Chadaide et al. [14] who studied the effect of tDCS on TMS-elicited PTs. While baseline PTs and their decrease induced by anodal tDCS were normal in 16 migraineurs (nine with aura), cathodal stimulation, which increased PTs in healthy controls, was not effective in patients.

LTP- and LTD-dependent plasticity abnormalities on the perceptual level have also been detected in migraine patients also by using psychophysical methods. Indeed, patients with episodic migraine with aura and chronic migraineurs were found less prone to TMS-induced suppression of perceptual accuracy in letter recognition than patients with migraine without aura and healthy subjects [15–20]. Another way to assess cortical inhibition is the evaluation of perceptual suppression of a single target using metacontrast masking. This is a type of visual masking that occurs when judgments about a target, like a letter, are impaired because of a subsequently presented, spatially non-overlapping mask, like a ring placed around the letter. Metacontrast masking was less suppressed in migraine patients with aura [21], compared to those without aura [22, 23].

Brighina et al. [24] used sound-induced flash illusions (SIFI) to study excitability of the visual cortex in healthy controls and two groups of migraine patients with and without aura, during and between attacks. The perception of multiple flashes ("fission" illusion) was reduced or abolished in patients with migraine, especially during an attack, while the number of perceived flashes ("fusion" illusion) was less consistently reported, but not disrupted, in patients. They concluded that the results support the dysfunctional multisensory integration in migraine. Cathodal tDCS over the visual cortex can increase the SIFI in healthy subjects, probably by decreasing cortical excitability. However, in contrast to these attenuated SIFI in healthy subjects and in line with the results of other studies using neuromodulatory methods in migraine [12, 14], cathodal tDCS was unable to modulate SIFI in patients reliably [25]. In another study, in which VEPs were co-recorded parallel with MRI spectroscopy, before any stimulation, migraineurs showed significantly higher glutamate/creatine ratios than healthy subjects [26]. In healthy subjects, anodal tDCS induced an increase and tDCS a decrease in this ratio. Photic stimulation reversed the changes in glutamate/creatine ratios, demonstrating homeostatic-like metaplasticity in the control group. Nevertheless, in migraine patients, both anodal and cathodal tDCS decreased the ratio. Furthermore, while healthy subjects showed an increase in VEP amplitude due to anodal and a reduction after cathodal tDCS, the modifiability of VEP under tDCS was reduced in migraineurs. The results imply a reduced and/or altered responsiveness of the occipital cortex to tDCS in migraine.

Overall, the studies reviewed above show a general deficit in cortical plasticity mechanisms, especially in inducing LTD or an abnormal LTP/LTD ratio in the visual cortex (Table 13.1).

13.3 Neuromodulation of the Sensorimotor Cortex in Migraine

In patients with migraine without aura, activation of the sensorimotor cortices with 10 Hz rTMS increased the amplitude of the early N20 somatosensory evoked potentials (SSEPs) and delayed habituation over successive blocks of responses. Using1 Hz rTMS no effects were observed [27]. This was subsequently also confirmed by a study of 10 Hz rTMS toward sham stimulation, where the neurophysiological change induced by real rTMS on SSEPs correlated with the reduction in headache severity, but not with the change in headache frequency in a group composed of mixed episodic and chronic migraine patients [28]. The enhancement of the excitability of the sensorimotor cortex with rTMS was also able to forcedly increase the interictal low thalamocortical loop activity in migraine, as assessed by the recording of the high-frequency somatosensory activity embedded in the common SSEP [27]. Interestingly, daily sessions of 10 Hz rTMS over the sensorimotor cortex reduced plasma glutamate levels and relative expression of *N*-methyl D-aspartate receptor subtype 2B (NR2B) [29] and increased plasma β

Table 13.1 Studies on modulation of visual cortex in migraine

Authors	Subjects	Methodology	Outcome's variables	Results
Brighina et al. [12]	15 HV 13 MA	1 Hz rTMS over V1	PT	↑ PT in HV ↓ PT in MA
Bohotin et al. [8]	24 HV 20 MO 10 MA	1 or 10 Hz rTMS over V1	VEP amplitude and habituation	↓ VEP habituation after 1 Hz rTMS in HV ↑ VEP habituation after 10 Hz rTMS in M
Fumal et al. [11]	8 HV 8 MO	Daily sessions of rTMS (1 Hz in HV, 10 Hz in MO)	VEP amplitude and habituation	Long-lasting ↓ VEP habituation after 1 Hz rTMS in HV Short-lasting ↑ VEP habituation after 10 Hz rTMS in MO
Chadaide et al. [14]	9 HV 16 M (9 MA)	Anodal or cathodal tDCS over V1	PT	↓ PT after anodal tDCS in HV and M ↑ PT after cathodal tDCS in HV, but not in M
Siniatchkin et al. [26]	10 HV 10 MA	Anodal or cathodal tDCS over V1	VEP amplitude	↑ VEP amplitude after anodal tDCS in HV ↓ VEP amplitude after cathodal tDCS in HV Anodal or cathodal tDCS was unable to induce significant VEP changes in MA
Viganò et al. [9]	11 HV 13 MO	Anodal tDCS over V1	VEP amplitude and habituation	↑ VEP habituation after tDCS in HV and MO
Omland et al. [13]	32 HV 32 MO	10 Hz rTMS over V1	VEP amplitude and habituation	↓ VEP habituation after rTMS in interictal MO (using large checks) ↑ VEP habituation after rTMS in interictal MO (using small checks)
Cortese et al. [10]	18 MO	Anodal tDCS over the left TP	VEP and SSEP amplitude and habituation	↑ VEP habituation after real tDCS in MO, but not after sham. No effects on SSEP
Maccora et al. [25]	11 MO 11 MA	Cathodal tDCS over V1	Perception of the sound-induced flash illusion (SIFI)	tDCS was unable to modulate SIFI in migraine

HV healthy volunteers, *M* patients with migraine, *MO* migraine without aura, *MA* migraine with aura, *PT* phosphene threshold, *rTMS* repetitive transcranial magnetic stimulation, *SSEP* somatosensory evoked potential, *TP* temporal pole, *V1* primary visual cortex, *VEP* visual evoked potential

endorphin [30], glutathione (an antioxidant marker), and total antioxidant activity levels [31] in migraine.

The same paradoxical effects of inhibitory and excitatory rTMS described for visual neuromodulation were also observed when the activity of sensorimotor

cortex was modulated, especially in migraine with aura [32–36]. Brighina and coworkers observed that 1 Hz rTMS at 90% of the resting motor threshold (RMT) delivered over the motor cortex paradoxically enhanced, rather than diminished, intracortical facilitation [32]. Two independent research groups showed that the neuromodulatory effects of rTMS depend on the intensity of the stimuli. In fact, trains of 5 Hz rTMS delivered at 110% and 120% of the RMT over the motor cortex induced short-term potentiation more easily in patients with migraine with aura than in those without aura and healthy controls [33, 35]. On the contrary, the same authors observed a progressive decrease in MEP size in migraine with aura patients during trains of 5 Hz rTMS at 130 % of RMT, which was in contrast to the clear MEP facilitation seen in healthy controls [33]. The authors interpreted these results in the light of a compensatory mechanism of homeostatic cortical metaplasticity: an excessive forced increase in cortical excitability by high-frequency and high-intensity trains elicited a compensatory mechanism of response inhibition. Consistent with other evidence obtained from studies recording cortical evoked potentials when other sensory modalities are targeted [7], the MEP response to 5 Hz rTMS trains strongly depended on the time window in which the patients have been studied along the migraine cycle [37], on attacks frequency, and if a given patient had medication overuse [37, 38]. Cosentino et al. [37] reported a pre-ictal excessive increase in MEP response during 5 Hz rTMS trains at 120% RMT, as opposed to an ictal and post-ictal inhibition of MEP. Similarly, diminished response was observed in patients with chronic migraine, who had background headache during evaluation. In a study using the same methodology, decreased MEP amplitudes were detected in patients with medication overuse headache (MOH) but not in patients with chronic migraine, helping to differentiate these two forms of headache [38]. Interestingly, in patients with MOH, the physiological short-term potentiating effect of 5 Hz trains of TMS on MEP amplitudes was restored after withdrawal from drug overuse parallel to the reduction of monthly headache days [39].

A way to study an aspect of LTP/LTD mechanisms is by coupling a peripheral nerve stimulation and cortical stimulation, a paradigm called paired associative stimulation (PAS). In healthy subjects, it has been seen that if the magnetic stimulus is delivered over the motor cortex before the sensory information reaches the parietal cortex, with around 10 ms difference, the excitability of the sensorimotor cortex decreases, but if the interstimulus interval is longer than the time needed to reach the parietal cortex, like around 25 ms, the excitability of the sensorimotor cortex increases. In patients with migraine without aura, Pierelli et al. using PAS paradigms found that inhibiting PAS paradoxically increased MEP amplitudes instead of decreasing them, and facilitatory PAS induced only a slight non-significant change [40]. Interestingly, in a small group of subjects, the authors observed that the inhibition PAS-induced changes (MEP increases) were inversely related to the degree of thalamocortical activation, as assessed by analyzing somatosensory high-frequency oscillatory activity.

That a dysfunctional thalamocortical activity during the interictal period may provide a possible explanation for the paradoxical effects induced by neuromodulatory procedures is also emphasized by the finding that the thalamocortical activity correlates with motor responses related to somatosensory cholinergic activity in healthy subjects, but not in migraineurs [41]. The phenomenon of short-latency afferent inhibition (SAI) consists in a peripheral sensory afferent volley conditioning the homotopic muscle response obtained by TMS over the motor cortex [42]. The peripheral electrical conditioning stimulus inhibits the MEP; the degree of this inhibition depends on the interval between the sensory and the motor stimuli (ISI). Studies in healthy humans showed that SAI is subject to the excitatory effect exerted by cholinergic thalamocortical afferents on inhibitory GABAergic cortical networks [42]. When ISIs were predetermined and equal in all subjects, SAI was reported to be decreased during the pre-ictal and ictal phases of episodic migraine [43], whereas, when SAI has been recorded at four different ISIs personalized on the basis of the individual SSEP N20 latency, SAI was reduced in patients between attacks compared to healthy volunteers, while it was enhanced during an attack [41].

To sum up, the electrophysiological data are, once again, in line with the data shown above, which emphasize a general dysfunction of the LTP and LTD mechanisms, characterizing the migraine brain [12, 32–37] (Table 13.2).

Table 13.2 Studies on modulation of sensorimotor cortex in migraine

Authors	Subjects	Methodology	Outcome's variables	Results
Brighina et al. [32]	8 HV 9 MA	1 Hz rTMS (90% RMT) over M1	MEP amplitude	↓ intracortical facilitatory circuits in HV ↑ intracortical facilitatory circuits in MA
Conte et al. [35]	19 HV 18 MO 19 MA	Train of 5 Hz rTMS (120% RMT) over M1	MEP amplitude	↑ MEP amplitude facilitation in MA MEP amplitude unchanged during migraine attack in three patients
Brighina et al. [33]	18 HV 18 MA	Train of 5 Hz rTMS (110 and 130% RMT) over M1	MEP amplitude	110% RMT: Facilitatory effect on MEP amplitude in MA, but not in HV 130% RMT: Inhibitory effect on MEP amplitude in MA, facilitatory in HV

(continued)

Table 13.2 (continued)

Authors	Subjects	Methodology	Outcome's variables	Results
Coppola et al. [27]	13 HV 13 MO	1 or 10 Hz rTMS over SM	SSEP amplitude and habituation, thalamocortical HFOs	↓ SSEP amplitude and habituation after 1 Hz rTMS in HV ↑ SSEP amplitude and habituation and HFOs after 10 Hz rTMS in M
Pierelli et al. [40]	15 HV 16 MO	Excitability enhancing and inhibiting paired associative stimulation (PAS)	MEP amplitude	↓ and ↑ MEP amplitude after inhibiting and enhancing PAS, respectively, in HV ↑ and ↓ MEP amplitude after inhibiting and enhancing PAS, respectively, in MO
Cosentino et al. [37]	20 HV 66 MO (36 interictal, 10 pre-ictal, 10 ictal, and 10 post-ictal) 48 MA (27 interictal, 7 pre-ictal, 7 ictal, and 7 post-ictal) 14 CM	Train of 5 Hz rTMS (120 % RMT) over M1	MEP amplitude	↑↑ of MEP during the pre-ictal period ↓ of MEP during the ictal and post-ictal period ↓ of MEP during CM
Kalita et al. [28]	56 (real) 38 (sham) Mixed MO and CM	10 Hz rTMS over SM or sham	SSEP amplitude and habituation	↑ SSEP amplitude and habituation with ↓ severity of headache
Misra et al. [30]	93 mixed MO and CM	10 Hz rTMS over SM or sham	Plasma β endorphin	↑ plasmaβ endorphin
Tripathi et al. [31]	150 mixed MO and CM	10 Hz rTMS over SM or sham	Glutathione and total antioxidant activity levels	↑ glutathione and total antioxidant activity levels
Tripathi et al. [29]	130 mixed MO and CM	10 Hz rTMS over SM or sham	Plasma glutamate levels, N-methyl-D-aspartate receptor subtype 2B (NR2B)	↓ plasma glutamate levels, relative expression of NR2B
Cortese et al. [38]	16 HV 16 CM 16 MOH	Train of 1 or 5 Hz rTMS (120 % RMT) over M1	MEP amplitude	↓ MEP amplitude during 1 Hz trains in all groups ↑ MEP amplitude during 5 Hz trains in CM and HV, but ↓ in MOH

(continued)

Table 13.2 (continued)

Authors	Subjects	Methodology	Outcome's variables	Results
Cortese et al. [39]	16 HV 13 MOH	Train of 1 or 5 Hz rTMS (120 % RMT) over M1 before and after acute medication withdrawal	MEP amplitude	↓ MEP amplitude during 5 Hz trains in MOH Restoration of normal ↑ MEP amplitude after drug withdrawal, in proportion with reduction of monthly headache days
Alaydin et al. [43]	16 HV 25 MO (10 interictal, 5 pre-ictal, 10 ictal)	Short-latency afferent inhibition (SAI)	MEP amplitude	↓ SAI during the pre-ictal and ictal phases
Coppola et al. [41]	16 HV 32 MO (16 interictal, 16 ictal)	Short-latency afferent inhibition (SAI)	MEP amplitude	↓ SAI between attacks ↑ SAI during an attack

CM chronic migraine, *HV* healthy volunteers, *M1* primary motor cortex, *M* patients with migraine, *MA* migraine with aura, *MEP* motor evoked potential, *MO* migraine without aura, *MOH* medication overuse headache, *RMT* resting motor threshold, *rTMS* repetitive transcranial magnetic stimulation, *SM* sensorimotor cortex, *SSEP* somatosensory evoked potential

13.4 Conclusions

Studies using rTMS and tDCS have consistently reported abnormal brain plasticity manifesting as paradoxical effects in response to both inhibitory and facilitatory neuromodulation, more evidently in migraine with aura [6, 7, 9, 10, 16]. In addition, several studies showed that the effect of a given protocol highly depends on the phase of the migraine cycle and undergoes further changes depending on the frequency of attacks and medication overuse. Because of this wide variability in the degree of cortical excitability of the brain in migraine patients, the best term to describe these phenomena is a "dys-excitability," or abnormal excitability, rather than hypo- or hyper-excitability. This altered excitability is characterized by the abnormal synaptic activity-dependent plasticity, mainly affecting LTD.

Whether these anomalies of synaptic plasticity can be generalized to all sensory modalities [7] remains to be determined. Furthermore, it should be also clarified how they are related to a dysfunctional thalamocortical pre-activation in migraine [27, 44–47],

Transcranial neuromodulation techniques can be effective in normalizing the abnormal interictal visual and sensorimotor information processing in migraine. Therefore, despite the lack of standardized stimulation paradigms and the lack of large, double-blinded sham-controlled trials, they can be tailored to the patient's pathophysiological profile and can be used as preventive treatment of episodic and chronic migraine [5, 48–50].

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Chapter 14
Neurophysiology of Migraine with Aura

Anna Ambrosini and Gianluca Coppola

Abbreviations

AEP	Auditory evoked potential
BAEP	Brainstem auditory evoked potential
CSD	Cortical spreading depression
EEG	Electroencephalography
EMG	Electromyography
EP	Evoked potential
ERP	Event-related potential
FHM	Familiar hemiplegic migraine
HFO	High-frequency oscillation
MA	Migraine with aura
MEG	Magnetoelectroencephalography
MEP	Motor-evoked potential
MO	Migraine without aura
nBR	Nociceptive blink reflex
PA	Persistent aura
PD	Photic driving
rTMS	Repetitive transcranial magnetic stimulation
SFEMG	Single-fibre electromyography
SSEP	Somatosensory evoked potential
SS-VEP	Steady-state visual-evoked potential
TCD	Thalamo-cortical dysrhythmia
TMS	Transcranial magnetic stimulation
VEP	Visual-evoked potential

A. Ambrosini
IRCCS - Neuromed, Headache Clinic, Pozzilli, Isernia, Italy
e-mail: anna.ambrosini@neuromed.it

G. Coppola (✉)
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome
Polo Pontino, Latina, Italy
e-mail: gianluca.coppola@uniroma1.it

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14.1 Introduction

The neurophysiological peculiarities of the migrainous brain, possibly forming the basis of predisposition to recurrent migraine attacks, have been extensively explored during the past 50 years. Electrophysiological patterns have been detected between migraine attacks and have been found to fluctuate depending on the duration of the interval between the previous and next attack, i.e. the migraine cycle. These are usually more pronounced amongst the migraineurs who experience aura; nevertheless, these patients have been less frequently studied from a neurophysiological point of view, possibly due the lower prevalence of migraine with aura (MA), in comparison to the commonest migraine without aura (MO). The migraine aura is commonly thought to be due to an electrocortical phenomenon known as cortical spreading depression (CSD). This is described as a wave of neuronal hyperactivity followed by a wave of hypoactivity, spreading slowly (3 mm/min [1]), postero-anteriorly, and reaching the parietal and/or temporal lobes. Although first described in animals by Leão [2], at present, the only indirect evidence for CSD in migraine with aura patients derives from functional MRI [3–5] and magnetoencephalographical [6, 7] studies. In animal models, CSD is able to ignite the trigeminovascular system, which, when translated to humans, could be responsible for the initiation of a migraine headache. However, little is known about predisposition for the generation of CSD and the possibility of detecting neurophysiological markers interictally.

Considering that the cortical areas implicated in CSD are particularly implicated in sensory processing, several independent research groups have consequently investigated electrocortical signals during different phases of the migraine cycle using different sensory stimuli, or single or repetitive neuromodulatory techniques delivered over the scalp. Moreover, migraine with aura was also investigated with peripheral techniques, such as electromyography (EMG), in order to search for pathophysiologically relevant markers, albeit not directly implicated in the generation of CSD.

Many of these studies involved both migraineurs with and without aura, not only because patients suffering exclusively from migraine with aura are less prevalent than MO but also because for many researchers the two conditions of MO and MA are variable clinical manifestations of essentially the same genetic disorder [8]. In this section, we will provide a comprehensive overview of the findings of clinical electrophysiological studies in MA patients.

14.2 Data Overview

14.2.1 Electroencephalography (EEG)

The most frequently described electrocortical phenomena in migraine patients in the past 60 years are the so-called H response to flicker stimulation—also known as enhanced photic driving (PD)—and abnormal resting-state EEG rhythmic activity.

Enhanced PD of EEG—or H response—is obtained during intermittent photic stimulation using fast Fourier transform analysis on steady-state visual-evoked potentials (SS-VEPs) and is more prevalent in migraine patients than in healthy controls. The fundamental components of the EEG spectra are increased equally in both MA and MO [9, 10], predominantly in the temporo-parietal regions, with reduced interhemispheric coherence in fronto-temporo-parietal areas [9]. The same phenomenon has also been described in juvenile MA patients [10]. H-response shows a sensitivity of 86.4% and a specificity of 97.5% in MA and MO patients, but not in patients affected by migraine with brainstem aura (previously called 'basilar migraine') [11]. In a study by de Tommaso et al. [12], PD was significantly enhanced in both MO and MA groups with respect to controls, but MA patients showed more pronounced decreased phase synchronization during light stimulation between beta rhythms and higher Granger causality values—measuring the flow of information and connections across different brain areas—compared to MO patients. In two other studies, response to photic stimulation was less apparent in MA than in MO patients [13, 14].

In migraineurs with aura, during the interictal period, alpha rhythm and peak frequency asymmetries over the posterior regions, increased power in alpha rhythms [15] and widespread increase in delta [10] and theta [10, 15] total power were demonstrated, in comparison with healthy controls by quantitative analysis. In migraine patients with a pure visual aura, a reduction in alpha rhythms [16] or unilateral reduction of alpha and theta activity, mostly contralateral to the neurological signs, is seen [17]. In comparison with migraineurs without aura, in MA patients, a greater alpha peak power interhemispheric asymmetry, chiefly in the posterior regions, which was not related to the headache side, has been demonstrated [10, 18]. When applied to migraine patients, electroencephalography (EEG) and magnetoelectroencephalography (MEG) techniques to demonstrate functional connectivity produced very interesting results: (a) a resting-state effective neural connectivity EEG study demonstrated a higher flow of information transfer in the beta band in MA patients, compared with MO patients and controls [19]; (b) in MA patients, a checkerboard pattern for visual stimulation produced an increase in transfer entropy with a higher density of information flow in the frontal regions in all the bands of rhythmic activity, compared with MO patients [19]; (c) in an MEG study, migraineurs with aura showed a significantly increased functional connectivity in the theta (4–8 Hz) band in the occipital area as compared with migraineurs without aura [20]. Furthermore, neuroimaging by the method of resting-state functional MRI confirmed that frontal and occipital networks showed functional connectivity anomalies particularly relevant in migraine [21–23].

In summary, even though PD is the most widely known EEG pattern correlated to migraine, resting electric and magnetic activity seems to better characterize migraine patients and better differentiate MA from MO patients than PD.

14.3 Evoked Potentials

Extracting—with the help of the averaging technique—cortical potentials evoked by external stimuli (EP) from the EEG signal has greatly assisted investigations in

almost all neurologic diseases. Migraine patients have been largely included in many of these studies since their conception. An enormous amount of studies have been published up to now, aiming to demonstrate whether the migrainous brain reacts differently to external repetitive sensory (visual, auditory and somatosensory) stimulations than the brain of subjects not suffering from migraine.

14.3.1 Grand-Average EP Amplitude

Evoked potentials are better analysed and studied when the single trigger-related sweeps (trials) are averaged with respect to the trigger. As visual symptoms are the most frequent features of the migraine aura, visual stimuli are the most often employed triggers for investigating evoked potentials. Most of the published studies using the classical method of averaging a large quantity of trials found increased amplitudes of steady-state (SS) or transient VEPs in MA patients interictally. In particular, using pattern-reversal stimulation, some researchers reported that the measured amplitudes of the grand average of VEP components N75-P100 and/or P100-N145 were greater in MA patients than in controls [24–29] and/or MO patients [24, 30, 31]. Similarly, the amplitude of SS-VEP harmonics is higher in migraineurs with aura, with respect to migraine without aura patients or healthy controls [32]. In contrast, other researchers reported reduced VEP amplitudes in MA patients [33], even when compared to MO [34]. Finally, many studies have shown VEP amplitudes in MA to be within the normal range [35–41].

Besides the visual cortex, other brain areas have been explored using grand-average evoked potentials in migraineurs. Somatosensory evoked potentials (SSEPs) disclosed a decreased amplitude of the prerolandic component (N20) in both MO and MA in one study [42], in contrast with other studies where it was within the normal range [43–45].

Exploring the auditory pathway, short-latency brainstem auditory evoked potentials (BAEPs) did not disclose any interictal abnormalities in migraine, possibly because patients with different migraine phenotypes (MO and MA, or different MA subtypes) were pooled in different proportions into a single group (see Table 5 in [46]).

Long-latency event-related potentials (ERPs) are thought to be the expression of the cognitive elaboration for the perception of an external stimulus. Amongst them, the auditory P300 is one of the most explored. In MA patients, an increased amplitude of the P300 was found in comparison to patients affected by other types of primary headaches [47, 48]. A similar result was reported for a mixed group of MO and MA patients, with respect to healthy controls. On the other hand, during mind wandering relative to on-task periods, the P300 amplitude was significantly reduced in migraineurs compared to controls, possibly as a compensatory strategy for reducing stimulus overload in the cortex [49].

In summary, most studies using EPs and ERPs indicate an increase in grand-average neural response to any kind of sensory stimuli in the MA group, suggested to be due to deficient short-term and long-term adaptive processes to external stimuli.

14.3.2 Interhemispheric Asymmetry

As the visual and somatosensory auras are usually unilateral, some researchers decided to investigate migraineurs with aura aiming to uncover asymmetries in their cortical responses. In fact, asymmetries were demonstrated for steady-state VEP amplitudes and transient VEP P100 amplitude distribution in the VEP N70 and SSEP N30 component amplitudes, both related [25, 50, 51] or not [52–54] with the side of visual aura.

Mean interhemispheric asymmetries of all BAEP peak latencies (except peaks IV and VI) were significantly increased in MO and MA patients (including some rare MA subtypes such as hemiplegic and brainstem migraine) with respect to healthy controls [55], but these results have not been confirmed [56].

14.3.3 Response Habituation

If the EEG traces representing evoked cortical responses to repetitive visual stimuli are not processed in total by a grand average but they are averaged only by small discrete consecutive blocks, in most studies VEP amplitudes tend to increase progressively instead of diminishing (i.e. deficient habituation) in MO and even more in MA patients, interictally [35–38, 40, 41, 57–59], even though this has not been confirmed by all researchers [26, 39, 60, 61]. One possible explanation for this phenomenon could be that lateral inhibitory mechanisms within the visual cortex might be malfunctioning, as suggested by a study where SS-VEPs were elicited by a windmill-dartboard pattern [37]. Using paired-pulse flash VEPs [62], impaired inhibitory mechanism functioning within the visual cortex was further confirmed in MA but not in MO patients.

Besides visual symptoms, many other neurological symptoms and signs may enrich the migraine aura, such as somatosensory, language, motor and balance impairment. Thus, the aura could manifest itself as very different phenotypes, which may be the expression of different pathophysiological mechanisms. In a study [63] where MA patients were divided into two subgroups according to the complexity of their aura (MA with exclusively visual aura and MA with complex aura, where, besides the visual aura, these patients also complained of somatosensory and/or dysphasic symptoms), VEP amplitude was significantly increased in MA with complex aura, possibly due to a genuine increase in cortical excitability, but it was within the normal range in migraineurs with exclusively visual aura. Lack of VEP habituation was present similarly in both groups, but interestingly it was positively correlated with the duration of the interval from the last migraine attack, only in migraineurs with complex auras, as already described in a mixed group of MO and MA [37].

An increased VEP amplitude and deficient habituation were also found in migraineurs with aura in comparison with controls, in a study where VEPs were co-recorded with MRI spectroscopy [64]. Both transcranial direct current stimulation procedures aiming to enhance and inhibit cortical excitability are able to

significantly potentiate and diminish VEP amplitude in healthy subjects, but cannot influence VEP amplitudes in migraineurs with aura [64].

Deficient habituation was largely detected interictally in migraineurs with aura by visual-evoked potentials [35–41], but was also found in SSEPs [65] and auditory evoked potentials (AEPs) [66], where it was responsible for the strong interictal dependence of AEPs on stimulus intensity [40, 66]. Impaired habituation was also found in cognitive potentials, as indicated by recording P300 amplitudes and latencies in MA [47, 48].

In summary, cortical evoked potentials help to testify that most migraineurs with aura have, to a greater extent than MO and in contrast to healthy subjects, higher cortical response amplitudes, increased interhemispheric response asymmetry and a deficit of amplitude decrement of responses to repeated stimulation.

14.4 Techniques of Neuromodulation

Migraine with aura was extensively investigated by using both single-pulse and repetitive transcranial magnetic stimulation (sTMS and rTMS). Most studies aimed to examine the effects on visual cortices, measuring prevalence and thresholds in TMS-elicited magnetophosphenes, but many studies have also been performed by stimulating primary motor cortices. Using single-pulse TMS, the thresholds for magnetophosphenes (PT) were significantly lower and their prevalence significantly higher in MA patients, in comparison with healthy controls in most [67–73] but not all [74–78] patients, suggesting higher cortical excitability levels in these patients. These findings were also confirmed in MA without headache when compared to patients suffering from transient ischemic attacks of vascular origin, suggesting occipital sTMS as a tool for discriminating one condition from the other in difficult differential diagnoses [79]. One study, where the sTMS test assessing PT was preceded by inhibitory rTMS over the primary visual cortex, showed that the phosphene threshold was normally enhanced in controls, but reduced in MA [76], but was normalized in these patients after prophylactic treatment with valproate [80].

Single-pulse transcranial magnetic stimulation on the primary cortices in migraineurs with aura showed greater motor-evoked potential amplitude in response to increasing intensity of stimuli, compared to controls, and its normalization after preventive treatment with levetiracetam [81]. Using trains of rTMS over the motor cortex delivered at an inhibitory frequency of stimulation, one study observed significant activation, rather than inhibition, of the intracortical facilitatory circuits in MA, possibly dependent on glutamatergic synaptic mechanisms [82], similar to the previously described study where V1 was investigated [80].

The same paradoxical effect was also demonstrated when an excitatory rTMS stimulation pattern was used. On the one hand, facilitatory rTMS over M1 can more easily recruit excitatory circuits in glutamate-dependent short-term synaptic potentiation mechanisms in MA, in comparison with MO and healthy subjects [83, 84].

On the other hand, excitatory rTMS over M1 determines a significant depression in the motor-evoked potential amplitude in MA, instead of MEP facilitation as is usual in healthy subjects [83].

As a matter of fact, both the paradoxical rTMS response and the deficient EP habituation suggest that in migraine patients, particularly those suffering from aura, malfunction of the synaptic plasticity mechanisms, which should prevent the immediate and longer-lasting cortical changes, reflects the adaptation to repeated stimulations. Further investigations should be able to determine whether this aberrant response of the cortex to neuromodulation is due to abnormal thalamic control [85] or inefficient hypothalamic functional connectivity, as recently suggested by a resting-state MRI observation in a single MA patient [86].

14.5 Electromyographic Techniques

Electromyographic techniques have been used in migraine particularly to explore the trigeminal system, although few studies have been performed in migraine with aura. Nonetheless, in these patients the techniques also permit the exploration of various incidental, possibly nonpathogenic, neurophysiological aspects.

Perrotta et al. [87] studied a group of MA patients between attacks by measuring the bilateral polysynaptic R2 component of the nociceptive blink reflex (nBR) in migraineurs with aura. In this study, MA and MO had comparable normal baseline activation in response to noxious supraorbital stimulation, but a lack of habituation of the nBR response in both MO and MA, with respect to controls. Surprisingly, the habituation deficit tended to be less pronounced in MA than in MO, and in the MA group it seemed to positively correlate with the frequency of the migraine attacks [87], similarly to that previously observed in MO patients [88]. In fact, a possible explanation for these results could be that patients with high attack frequency are more likely to undergo a test within a closer temporal proximity of a migraine attack—when the response habituation is normalized—with respect to patients where attacks are infrequent [89].

Following the discovery that a rare subtype of migraine aura, familial hemiplegic migraine 1, is due to a genetic mutation in the CACNA1A gene [90], which codes for the main subunit of the P/Q Ca^{2+} channel—particularly expressed presynaptically at the neuromuscular junction (NMJ)—some researchers performed single-fibre electromyography (SFEMG) in various phenotypically different MA patient subgroups, aiming to explore possible subclinical NMJ functional abnormalities that might correlate with that genotype. In fact, subtle subclinical dysfunction in neuromuscular transmission was detected in patients suffering from MA, in comparison with MO and healthy controls. Furthermore, these abnormalities were expressed more in patients with pure typical aura, with respect to those who experienced both MO and MA, and this was particularly pronounced in patients who reported complex—such as sensorimotor or dysphasic or balance impairment—aura symptoms [91, 92] and/or prolonged aura. These findings were confirmed in a

larger group of MA patients [93, 94], but surprisingly they were not in a small group of familiar hemiplegic migraine (FHM) patients [95].

Interestingly, in three MA patients, the mild SFEMG abnormalities found before treatment with acetazolamide was started disappeared after treatment, in parallel with clinical improvement [96].

14.6 Neurophysiological Findings During Migraine Aura

The transient phase of aura cannot be predicted or, easily and consistently, experimentally induced in humans, and, when spontaneously presenting, it usually lasts for 1 h at most. Thus, it is difficult to record patients during this phenomenon, and neurophysiological studies aiming to explore these cases are rare and mostly anecdotal.

Some studies have described mild asymmetry of slow waves in the fronto-temporo-occipital areas, contralateral to the visual field defect, during visual aura and/or early headache phase, which disappeared during the pain phase [97, 98], but in other studies the EEG under similar conditions was normal [99]. However, in some patients, identical EEG abnormalities were also found interictally [98].

Brain mapping investigations using topographic EEG and MEG mapping observed similar results, pointing to a slow, spreading modification of cortical activity, suggesting the occurrence of CSD. In one patient with complex aura, topographic EEG mapping showed a posterior-anterior spreading of slow activities and depression of alpha activity in the cortices contralateral to the neurological defective signs [17].

In another MA patient examined during a typical visual aura, MEG recording revealed alpha rhythm event-related desynchronization in the contralateral extrastriate and temporal cortex during the visual symptoms and gamma band desynchronization which reached its maximal expression in the 10 min following the aura [7]. Another MEG study described the occurrence of slow, direct current potential shifts during the aura, very similar to those observed during CSD in animals [100], and similarly spontaneous and visually induced migraine aura eliciting an abnormal spread of visual-evoked activity [6].

The visual lateralized aura induces contralateral suppression or complete abolition of the first three components of the flash VEPs [101] and of the parietal component of the SSEPs [102], together with delayed latency and increased central conduction time of the latter SSEP component [102]. All of these neurophysiological abnormalities gradually normalized during the headache phase [101, 102].

In a group of six patients investigated during persistent aura (PA) without infarction, the P100 MEG response to checkerboard pattern reversal was earlier and more intense than in MO, MA, ictal migraineurs and chronic migraine. Furthermore, in these patients the deficit of P100m habituation to repeated stimuli was more pronounced than in MO and MA patients, interictally [58].

14.7 Neurophysiological Findings in Other Non-common Auras

The aura phase could last as long as days in hemiplegic migraine; thus, despite the low prevalence of this disease, neurophysiological studies have been extensively performed, in particular EEG investigations. Most of these studies described EEG abnormalities during acute attacks of hemiplegic migraine, such as unilateral or bilateral delta EEG activity—sometimes spreading postero-anteriorly [103]—and a reduction of alpha [104–113], whereas theta abnormalities were observed interictally in hemiplegic migraineurs [107, 114].

In migraineurs with brainstem aura (previously termed basilar-type migraine), whether their aura is characterized by the presence of disturbed consciousness, severe clinically relevant EEG-slowing or generalized spike and wave complexes have been described, and they can last for several days [115–125].

A small group of nine FHM patients (FHM-1 $n = 5$; FHM-2 $n = 4$) underwent an EP investigation where VEPs and nBR habituation and IDAP were measured, and the results were compared to those in a group of seven healthy controls. In contrast with MO and MA patients, migraineurs affected by FHM did not have a reduced, but rather more pronounced, interictal VEPs and nBR habituation in comparison with healthy subjects, and no differences were found in IDAP, besides a trend for the slope to be steeper in FHM patients [126].

Another study confirmed that FHP patients have a paradoxical neurophysiological behaviour when compared to that shown in the commoner form of migraine with typical aura. In ten FHM patients who underwent TMS in the primary motor area during a hemiparetic aura, higher resting motor threshold, longer central conduction time and lower MEP amplitude on the ictally paretic side than on the non-affected side were described, whereas in contrast, MEP amplitude was significantly increased in a group of migraineurs with typical aura [127].

14.8 Discussion

At present, there is no general consensus regarding which brain structures activate, leading to the cascade of events resulting in the migraine aura, neither in terms of the factors that initiate such activation nor the characterization of the link between the aura phenomenon and the initiation of the pain phase. Nonetheless, experimental evidences suggest that CSD waves induce the sequential activation of first-order or second-order trigeminovascular nociceptors [128]. It is plausible that the pain modulatory structures in the brainstem, such as the raphe magnus, the locus coeruleus and other aminergic nuclei, are susceptible to a cyclical recurrent malfunction which could be responsible of the sequential events that result both in the starting of CSD and the onset of headache [129, 130]. There is much evidence that the

brainstem is particularly involved in migraine pathogenesis. One study demonstrated a hyperperfusion within the brainstem during migraine aura [131] and that the same area seems to be involved in the generation of attacks in MO patients [132, 133] or a mixed group of MO and MA patients [134, 135]. Besides the brainstem, several cortical and subcortical areas, such as the neurolimbic area [136], periaqueductal grey matter [137], hypothalamus [86], thalamus [138], trigemino-thalamic tract [137] and visual [131, 139] and somatosensory [140] cortex, exhibit abnormal macrostructure and impaired functional activation. It is clear that a large variety of brain structures are implicated in MA pathophysiology, as shown by the neurophysiological studies reviewed in this chapter. However, a weakness in most published studies where neurophysiological techniques are used to investigate migraine with aura is that they do not disclose whether the patients included in the MA groups suffered exclusively from migraine with aura or whether they had also migraine without aura. This is quite an important point, as some studies, e.g. the ones using SFEMG, demonstrated that patients with MO and MA had more pronounced abnormalities than patients who manifested only MO, but were milder in comparison with patients affected exclusively by MA. This could explain some of the questionable and uncertain results presented in this chapter.

As a general summary, neurophysiological studies in MA have shown that:

- Most quantitative EEG studies reported enhanced interictal photic driving, or 'H-response', and an increase of slow and hyper-synchronized alpha rhythmic activity.
- As a general rule, EP and ERP studies witness a cortical hyper-reactivity to sensory stimuli, including cognitive stimuli, which presents itself as an increase in cortical responses, which, when described, was higher in MA than in MO patients.
- An interictal abnormal sensory processing, suggested by deficient habituation, lack of cortical inhibition and paradoxical responses to neuromodulation, has been described in MA (Table 14.1). These abnormalities seem to be positively correlated in MA patients to the duration of the time interval between the last and the next migraine attack, similar to that demonstrated in migraineurs without aura.
- The clinical aura features are numerous and could present to different extents; thus, migraine with aura is more likely to represent a spectrum of clinical entities expressing different pathophysiological disorders, rather than a single disease. As a matter of fact, the neurophysiological patterns manifest themselves in different ways in patients experiencing pure visual auras, with respect to those with prolonged, somatosensory, dysphasic or motor auras.
- Few investigations were performed in patients whilst they were experiencing an aura (Table 14.2). In general, they showed unilateral abnormalities of cortical electrogenesis—possibly the expression of an underlying metabolic abnormality [141]—desynchronized visual and somatosensory potentials, signal desynchronization in extra-striate and temporal regions with MEG and large variations in direct current potentials. These abnormalities are very similar to those illustrated

Table 14.1 Common neurophysiological findings in episodic migraine with aura in between attacks

	Episodic migraine with aura between attacks
Neurophysiological tool	
Electroencephalography	• Enhanced photic driving during intermittent photic stimulation • Abnormal electroencephalographic rhythmic activity at rest • Alpha rhythm and peak frequency asymmetries over the posterior regions • Increased power of alpha and presence of slowing (delta, theta) rhythmic activities
Magnetoencephalography	Abnormal electroencephalographic rhythmic activity at rest
Grand-averaged evoked potentials and event-related potentials	• Increased amplitudes of steady-state or transient visual evoked potentials (more pronounced than in migraine without aura) • Interhemispheric amplitude asymmetries in response to visual and auditory stimulations (sometimes related with side of aura symptoms) • Reduced activity of somatosensory thalamo-cortical afferent loops
Evoked potentials and event-related potentials amplitude habituation during repetitive stimulation	• Reduced amplitude habituation (sometimes more pronounced in migraine without aura) during sustained visual, auditory, somatosensory and cognitive stimulations
Single-pulse or repetitive transcranial magnetic stimulation (TMS)	• Lower thresholds for evoking magnetophosphenes • Paradoxical effects in response to cortical excitability enhancing and reducing paradigms of TMS
Electromyographic recordings	• Deficit of habituation of nociception-specific blink reflex • Subclinical abnormalities of neuromuscular transmission on single-fibre electromyography

in animal models during CSD, suggesting the occurrence of such a phenomenon also during aura in humans.

– Surprisingly, the few investigations performed in FHM patients using cortical and brainstem evoked potentials and SFEMG did not produce results similar to MO and MA patients, but closer to those obtained in healthy subjects, suggesting that this subtype of migraine is probably not part of the migraine spectrum, but more likely a syndrome in which the migraine attack is only a partial manifestation of the disease [142] (Table 14.3).

In our opinion, the neurophysiological patterns described in migraine patients, and particularly those suffering from MA, characterized by abnormal cortical rhythmic activity, increased cortical responsivity and deficient lateral inhibition may be caused by 'thalamo-cortical dysrhythmia' (TCD) [36], already suggested to underpin numerous functional brain disorders [143]. According to the TCD theory, a

Table 14.2 Common neurophysiological findings in episodic migraine patients during the aura phase

	Episodic migraine during the aura phase
Neurophysiological tool	
Electroencephalography	• Slight asymmetry of slow waves in the fronto-temporo-occipital areas contralateral to the visual field defect
Magnetoelectroencephalography	• Alpha and gamma rhythm event-related desynchronization contralateral to the visual field defect • Slow direct current potential shifts, very similar to those observed during experimentally induced cortical spreading depression in animals
Grand-averaged evoked potentials and event-related potentials	• Reduced amplitude or complete abolition of cortical evoked potentials in the hemisphere contralateral to the visual field defect
Evoked potentials and event-related potentials amplitude habituation during repetitive stimulation	• Deficient habituation in patients experiencing persistent aura without infarction

Table 14.3 Common neurophysiological findings in migraine with brainstem aura (BA) and familiar hemiplegic migraine (FHM) patients

	Non-common forms of migraine with aura
Neurophysiological tool	
Electroencephalography	• BA: Serious and clinically relevant focal electroencephalographic-slowing or generalized spike and wave complexes that may last for several days • FHM: Presence of unilateral or bilateral delta rhythmic electroencephalographic activity (sometimes spreading postero-anteriorly) and reduced alpha activity
Evoked potentials and event-related potentials amplitude habituation during repetitive stimulation	• FHM: Contrary to what is observed in the most common forms of migraine with aura, FHM patients showed more pronounced habituation during visual evoked potentials recording than control subjects
Single-pulse transcranial magnetic stimulation (TMS)	• FHM: Higher resting motor threshold, longer central conduction time and reduced motor-evoked potential amplitude on the ictally paretic side
Electromyographic recordings	• FHM: Contrary to what is observed in the most common forms of migraine with aura, FHM patients showed more pronounced habituation during nociception-specific blink reflex recording than control subjects

functional disconnection of the thalamus from subcortical areas (such as the brainstem monoaminergic nuclei) induces a change in rhythmic thalamo-cortical activity, which may favour low-frequency activity at the cortical level. As a consequence, at the beginning of stimulation, the firing rates of excitatory pyramidal cells decrease, and the firing rate of fast-spiking inhibitory interneurons reduces during stimulation

[144]. Supporting this theory, the amplitude of the pre-synaptic burst of high-frequency oscillatory activity embedded in the common SSEPs, reflecting thalamo-cortical activity, tends to decrease [44] or is definitely reduced [43] in MA patients, interictally. In another study, migraineurs with aura had an increased early high-frequency oscillation (HFO) activity embedded in the common VEPs, when compared to MO and healthy subjects. Furthermore, a deficient habituation in cortical visual HFOs was found both in MO and MA patients, which is also in line with the TCD theory [36]. The anatomical substrates of the deficit in thalamic control in migraine with aura have been recently explored [137–139, 145], and this phenomenon seems to be dynamically related to the time interval from the last migraine attack [146].

14.9 Conclusions

A small number of neurophysiological patterns seem to be peculiar to migraine with aura, as many of these are shared with migraine without aura, though in MA they seem to be more pronounced. As suggested before, we surmise that this is due to the inclusion of groups of patients suffering both from MO and MA in the migraine with aura group, which may have obscured the effective differences between these migraine subtypes [8]. Moreover, pharmacological studies have demonstrated that some drugs can halt the aura, but not the start of the migraine pain, whereas clinical experience indicates that precocious symptomatic treatments may prevent the headache phase but not the aura evolution. This indicates that the aura and the headache pain are likely two distinct and separate phenomena, from a pathophysiological viewpoint [147]. Genetic studies have failed to demonstrate that the genes involved in the pathophysiology of monogenic subtypes of migraine aura, such as FHM, are involved in the common forms of migraine with aura [148]. Furthermore, the peculiar neurophysiological behaviour demonstrated in FHM suggests that this condition cannot be definitely included in the migraine spectrum. Genome-wide association studies (GWAS) have shown that some genetic variants are associated with both MO and MA, but they cannot distinguish whether they are associated with the aura or migraine pain [8]. Moreover, the perfusion abnormalities accompanying migraine with aura have been found in MO patients, but they were seen during the pain phase and under intense visual stimulation, which casts doubts upon the possible auratic nature of the phenomenon [149].

Supplementary investigations are clearly needed in order to explain whether and how the neurophysiological patterns found in MA patients during and outside the aura phase are related. Thalamic/thalamo-cortical activity should be further explored in MA, searching for a possible correlation with migraine attack frequency and duration of the disorder, and studies should examine how this activity influences the manifestation of abnormal sensory processing in migraine.

Indeed, future studies need to identify possible correlations between clinical and neurophysiological phenotypes of migraine with aura, allowing the characterization of patients that could become targets for novel individualized treatments.

Lastly, investigations which couple functional neuroimaging and neurophysiological methods in the same patient could help to identify the effective and anatomical correlates of the abnormal cerebral information processing in migraine with aura.

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Chapter 15
Neurophysiology in Children and Elderlies with Migraine

Massimiliano Valeriani and Parisa Gazerani

15.1 Introduction

Neuroimaging and neurophysiologic methods have given a large contribution to the increase of our knowledge about migraine pathophysiology. While migraine has been considered for a long time a disease of the head vascular structures, it has been acquired that the cerebral cortex plays a key role in the cascade of events which trigger the migraine attacks [1]. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown the metabolic involvement of several brain regions known to process the nociceptive input [2]. More recently, changes in the architecture of cerebral cortices have been demonstrated by MRI during both the migrainous attack and the interictal period [3]. Although neuroimaging techniques provide a high spatial resolution, the use of the blood flow as a surrogate of the synaptic activity does not allow them to guarantee an equally good time resolution [4]. Moreover, blood flow changes can hardly let us know whether the underlying physiological event is due to increased or reduced excitability. In contrast, electroencephalography (EEG) and evoked brain potentials (EPs), though having less spatial accuracy than imaging, have the advantage of an excellent temporal resolution as these techniques measure the brain activity in real time on a millisecond scale [5]. Moreover, neurophysiologic methods can provide a measure of the excitability of both the sensory and motor areas of the brain [6, 7].

M. Valeriani (✉)
Headache Centre, Division of Neurology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark
e-mail: m.valeriani@tiscali.it

P. Gazerani
Biomedicine, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

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Most neurophysiologic studies on primary headache pathophysiology concern the adults, while migraine in children and elderlies has been far less studied. The neurophysiologic investigation in children is important for two main reasons: (1) some contrasting results in children and adults with migraine suggest that the pathophysiological background can change with the central nervous system development, and (2) migrainous children probably represent the best patients to study the pathophysiology of the disease, since the environmental influences, including drugs, are less important in childhood [8]. The same points, seen from another perspective, support the importance of neurophysiologic studies in elderlies: (1) migraine pathophysiological mechanisms depend not only on brain development but probably also on the modifications related to either normal aging or pathological degeneration, and 2) the brain dynamics which represent the target of the environmental factors, contributing to build the migrainous phenotype, are still unknown.

In this chapter, we will review the clinical neurophysiologic studies dealing with children and elderlies, considering the contribution provided by different techniques.

15.2 Neurophysiologic Studies in Children with Migraine

15.2.1 Abnormal Brain Excitability

Migraine is associated with a dysregulation of cerebral cortex excitability, which was variously demonstrated [9]. Among the sensory cortices, the visual area represents the most frequently studied brain region. Visual evoked potential (VEP) amplitude to both flash [10] and pattern-reversal [11–13] stimulation is higher in migraine children than in healthy subjects, thus confirming what had been previously found in adults [14, 15]. We can suppose that the increased VEP amplitude may be due to a reduced VEP habituation, which has been consistently demonstrated in adult migraineurs [16]. The phenomenon of habituation consists in a physiological decrease of the response of the sensory cortices to the arrival of a repetitive input. Surprisingly, while a reduced VEP habituation was reported by many studies in adults [17], it has been never demonstrated in young migraineurs [18]. In children with migraine, the primary somatosensory cortex excitability was investigated by calculating the recovery cycle of the somatosensory evoked potentials (SEPs) [19]. SEP recovery cycle is shortened in young migraineurs, thus suggesting a disinhibition at different levels of the central nervous system. This abnormality can be partially restored by an effective prophylactic treatment with topiramate [20].

15.2.2 Event-Related Potentials in Pediatric Migraine

The term “event-related potentials” (ERPs) commonly refers to partially or totally endogenous brain responses characterized by long latency and modification during cognitive tasks.

In migraine children, the visually evoked P300 shows increased amplitude, due to a reduced habituation, as compared to healthy controls [21]. Also P300 amplitude to both painful and non-painful mechanical stimuli is larger in migraine patients than in control subjects, although no difference in the P300 habituation is found between groups [22]. Valeriani et al. [23] showed that the auditory P300 and mismatch-negativity (MMN) habituation is lower in both migraineurs and tension-type headache (TTH) children than in control subjects. The last finding suggests that in pediatric age the abnormal brain excitability represents a common background for both migraine and TTH, thus suggesting that in children migraine and TTH are not distinct entities, but two aspects of the same spectrum of benign headache [24]. While in adult migraineurs the ERP habituation deficit is considered specific for migraine, it being absent in non-migraine headaches [25, 26], in pediatric age results are often conflicting [13, 21, 25, 27, 28]. Clinical studies showing that during childhood many TTHs may turn into typical migraines support the idea that migraine and TTH can be considered as one disease at this age [29, 30]. One interesting finding of the study by Valeriani et al. [23] is represented by the significant positive correlation between the P300 habituation deficit and some behavioral abnormalities, suggesting that in childhood the psychological factors are particularly important for the development of the migrainous phenotype (Fig. 15.1). The search for a correlation between psychological symptomatology and neurophysiologic features may be a promising way to solve the long-lasting question about the relative importance of psychological/environmental and organic/genetic factors in migraine pathophysiology.

15.2.3 Pediatric Migraine as a Maturation Disorder

Some neurophysiologic studies allowed us to interpret migraine as an abnormality of the developing brain maturation, even if the results are often in disagreement.

While in healthy subjects the early component of the contingent negative variation (CNV), a brain response representing the preparation to movement, reduces its amplitude and increases its habituation with aging, in migraineurs the CNV amplitude remains stable and its habituation is decreased [31]. The lack of the normal age-dependent CNV modification led Bender et al. [28] to interpret migraine as a maturation disorder (Fig. 15.2). In a series of studies, Oelkers-Ax [18, 32] showed that the modifications of some VEP components from the pre- to the post-puberty age are different between migraineurs and healthy subjects, thus suggesting a visual system maturation delay in migraine patients.

Iacovelli et al. [27] studied the N140 SEP component in migraine adolescents and found that its amplitude increases when subject's attention is addressed to the stimulated hand. This finding is similar to what is usually observed in normal adults [33], but it is different from the result obtained in healthy adolescents in whom the N140 amplitude is not modified by attention manipulations [27]. These data suggest that the psychophysiological mechanisms of spatial attention in young migraineurs are more similar to those of adults than to those of healthy children.

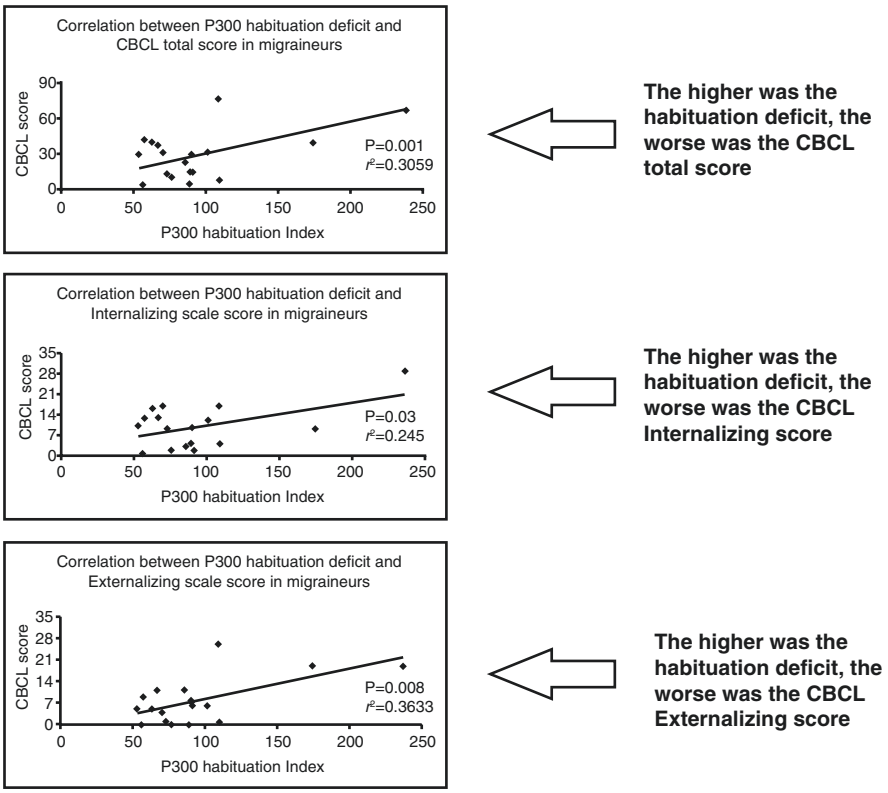

Fig. 15.1 Correlation between the P300 habituation deficit and the CBCL scores in children with migraine. The figure shows a direct correlation between the P300 habituation deficit and different CBCL scores (Modified from [23])

Also Buodo et al. [34], who studied the vertex negative response evoked by emotionally significant pictures, suggested a faster brain maturation in migraine children than in healthy controls.

15.3 Neurophysiologic Studies in Elderlies with Migraine

15.3.1 Migraine in Advanced Age

Traditionally, elderly has been defined as a chronological age ≥60 years [35]. Compared with 2019 (9 %), in 2050 one in six people in the world will be over age 65 (16 %), and in 2100 the percentage will rise to 23 % [36]. Global aging calls for further research on older adults to understand and overcome burden of health-associated challenges of aging [37]. Headaches are among medical conditions that

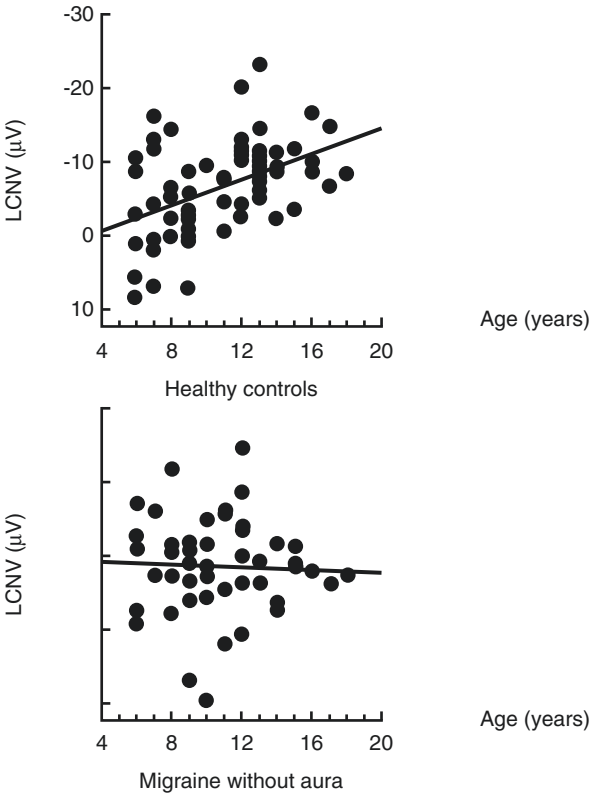

Fig. 15.2 Correlation between CNV amplitude and age in healthy controls (upper) and young migraineurs (lower). The lack of CNV amplitude increase with age in migraine is interpreted as a marker of maturation disorder (Modified from [28])

negatively affect elderly, and it is expected to continue as a burden to global aging [38, 39]. Prevalence of headache among elderly has been reported to be 12–50% [38, 39] with frequent headache (>2 attacks/month) up to 17% [40, 41]. Headache in elderly—specifically when the onset of headache occurs in older part of the age span—needs a thorough investigation for proper and correct diagnosis [42]. Some primary headaches, mostly hypnic headache [43], start after age of 50, in contrast to majority of primary headaches that start earlier in life. One of those is migraine that contributes to 0.5% of all new-onset headaches at 65 years and above [38, 44]. Besides newly diagnosed migraine in elderly, many of already diagnosed migraineurs continue to have migraine attacks in older age. A general belief exists that migraine improves by age or disappears. Studies in favor of this belief show that 40% of people with migraine no longer have attacks by 65 years. Another relevant finding is that before menopause, women have three times more migraine attacks than men, while after 60 years, this proportion drops to twice. A recent review concluded that the prevalence of migraine in older patients who are in their 60s and 70s is significant, even though both incidence and prevalence decrease with age [45]. Therefore, it is perhaps more accurate to state that migraine continues to occur in elderly, but its characteristics might differ from younger adulthood [46, 47].

To differentiate migraine in elderly, methods such as brain imaging and cerebrospinal fluid (CSF) analysis have been used to exclude other causes of headaches (secondary headaches account for 15% of the total headaches in the elderly) [38].

15.3.2 Neurophysiology of Migraine in Elderly

Several neurophysiologic tools can be used for migraine in elderly. Examples are EEG or magneto-EEG or MEG, a recording of spontaneous cerebral activity; EPs in response to visual, auditory, or painful stimuli; and the nociception-specific blink reflex (nsBR), an evaluation of trigeminal nociception. According to literature, majority of interictal recordings in young adults have shown a decreased habituation to repetitive stimuli of different modalities. These abnormalities at cortical and subcortical levels have been found to be normalized during headache phase of migraine and in the peri-ictal phase. Available findings from studies using a range of techniques suggest persistent changes in certain brain structures among chronic migraineurs, while fewer or transient changes occur in individuals with episodic migraine.

As for clinical neurophysiology of migraine in elderly, there is simply very little or no research in this area. Most studies have included adults below the age of 65. Among few studies on migraine in elderly, only one study has investigated the effects of pressure, heat, and cold pain thresholds in elderly patients [48]. This study did not find significant differences for pressure and cold pain thresholds at cephalic, cervical, and extracephalic regions between migraine patients and healthy controls. However, the migraine group showed significantly lower heat pain threshold in the upper neck area, which was mainly related to the presence of pain in the area [48].

Studies on relationship between headache and hormonal activity in elderly are also limited [44, 49]. The low estrogen level in elderly women may explain why onset of migraine in this age group is uncommon. Migraine with onset at older age affects women and men equally, while in younger age groups women outnumber men [50]. Collectively, it has been suggested that migraine without aura improves more frequently after menopause compared to migraine with aura. This can be a possible consequence of migraine without aura being more sensitive to female sex hormones [49]. Aura is considered a consequence of cortical spreading depression while pain is a neurovascular event outcome. Effects of female sex hormones on aura need further investigation. Male sex hormones might also have an influence on the course of headache disorders among elderly women. Only one case-control study assessed the levels of androstenedione and testosterone in the serum of postmenopausal women with and without migraine and found no differences in the levels of these hormones between groups [51].

A review article [52] has attempted to summarize evidence on neural plasticity in chronic headaches including chronic migraine (CM). Electrophysiological and neuroimaging studies have revealed different aspects of neural plasticity associated with chronic headaches, especially migraine. Based on the available studies,

it has been concluded that migraine chronification involves various aspects of neural plasticity in pain-related neural networks. Despite inconclusive findings in brain structures, earlier studies have characterized neural plasticity in association with CM evolution by brain excitability change (central sensitization, habituation change, impaired inhibition), altered biochemistry and metabolism, and aberrant functional connectivity. Some studies further suggest an ictal-like response pattern in interictal periods of CM patients. Taken together, it is assumed that chronic headache may be an abnormal functional status of never-ending headache underpinned by neural plastic responses to recurrent headaches. Genetic predisposition may also influence the evolution of chronic headaches. However, the true genetic effect upon neural plasticity can only be disentangled if the complex interaction between genes and electrophysiology or neuroimaging is clarified in future studies [52]. Although not directly linked to migraine in elderly, some of these neurophysiologic data of adult CM patients can be considered potentially valid also in elderly chronic migraineurs. However, one must consider that data might not be necessarily extrapolated and that, for the new-onset migraine in elderly, neurophysiologic data are still lacking.

15.4 Conclusion and Future Perspectives

Clinical neurophysiologic methods have been used to study migraine pathophysiology. These techniques are mainly flexible, non-invasive, and relatively inexpensive to apply. Neurophysiologic studies have overall documented the presence of changes occurring during the course of migraine. Inter- and intra-individual variability of neurophysiological recordings is high and explains why none of these techniques are suitable for diagnostic purposes in migraine. However, most neurophysiologic studies have contributed to a better understanding of migraine pathophysiology [9].

Future work in clinical neurophysiology of migraine can facilitate understanding of migraine susceptibility and its recurrence nature and consequently identifying of new pharmacological and non-pharmacological interventions. Limited information in children and adolescents with migraine and lack of information in elderly migraineurs call for further investigation in these special migraine populations. Methodological considerations are of great value to reduce variable studies outcome. Considering blind studies in recording and analysis, collecting clinical and headache diary data together with neurophysiologic testing, and exploring sleep, arousal, and attention factors in future protocols are encouraged. It has been proposed that neurophysiologic testing in migraine can help in phenotyping migraine patients for genetic and therapeutic studies. These techniques can also facilitate identification of dynamic functional changes that modulate the disorder over the age span and enhance our knowledge for chronification of migraine in relation to maladaptive features of central nervous system plasticity [52].

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Chapter 16
Neuroimaging Correlates of Neurophysiological Findings

Marco Lisicki and Wei-Ta Chen

16.1 Introduction

Neurophysiological and neuroimaging techniques complement each other when studying the brain. The high temporal resolution (i.e., the capacity to isolate rapidly occurring events) that characterizes neurophysiological analyses together with the high spatial resolution (i.e., the ability to precisely describe regions of the brain associated with an event) of imaging methods yields an integral perspective that can expand our understanding of cerebral processes. Given that they evaluate different aspects of brain dynamics, the interdependence between outcomes observed in neurophysiological and neuroimaging experiments is not necessarily always straightforward. Electromagnetic activity in the cortex, assessed through magnetoencephalography (MEG) and electroencephalography (EEG), results from simultaneous changes in membrane potentials of populations of neurons. Although not on a one-to-one relationship, such activity is accompanied by transient modifications in local blood flow and metabolism, which can be recorded using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or magnetic resonance spectroscopy (MRS). Furthermore, even transitory neuronal activation is capable of inducing structural brain changes that can be revealed using morphometric (MRI) neuroimaging techniques [1, 2]. Therefore, studying the consistency (or discrepancy) between the outcomes of

M. Lisicki
Neuroscience Unit, Headache Department, Conci•Carpinella Institute, Córdoba, Argentina

Headache Research Unit, Department of Neurology-Citadelle Hospital, University of Liège, Liège, Belgium

W.-T. Chen (✉)
Brain Research Center, National Yang-Ming University, Taipei, Taiwan

School of Medicine, National Yang-Ming University, Taipei, Taiwan

Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

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neurophysiological and neuroimaging experiments is fundamental to improve our comprehension of how the migraine brain works (Fig. 16.1).

In this chapter, we summarize the most important neuroimaging correlates of electrophysiological findings in migraine and briefly discuss their contributions to the advancement of our understanding of migraine pathophysiology.

16.2 Altered Sensory Processing

Patients with migraine are hyperresponsive to sensory stimuli [3]. This alteration has been separately evaluated in multiple electrophysiological and neuroimaging experiments in the past [4], using most (if not all) available stimulation paradigms.

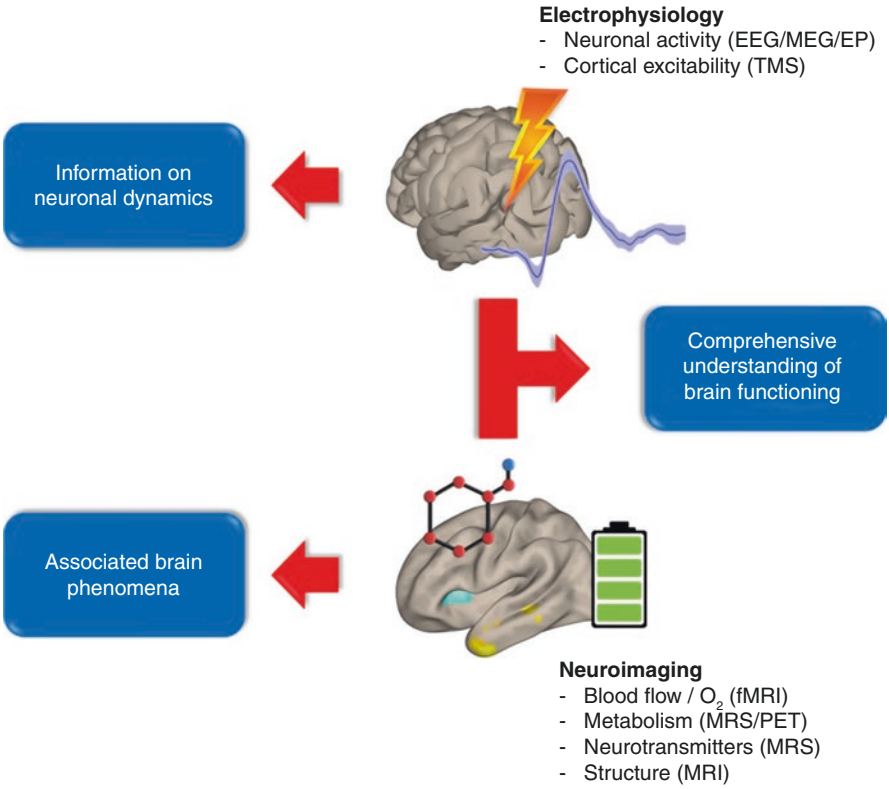

Fig. 16.1 Neurophysiological and neuroimaging methods each provide valuable information about different aspects of brain dynamics, but combining them achieves a truly comprehensive view of cerebral processes. This makes the interpretation of findings more straightforward and helps fill the gaps left by hypothetical associations. *EEG* electroencephalography, *MEG* magnetoencephalography, *EP* evoked potentials, *TMS* transcranial magnetic stimulation, *fMRI* functional magnetic resonance imaging, *PET* positron emission tomography, *MRS* magnetic resonance spectroscopy, *MRI* magnetic resonance imaging (in reference to MRI-based morphometric analyses)

Despite methodological differences, some degree of concordance between enhanced cortical responsiveness observed using electrophysiological techniques and the increased magnitude of surrogates of neural activation observed using functional neuroimaging tests has been recognized [4]. However, a combined electrophysiological and neuroimaging assessment of the same group of individuals has only been performed in a few studies. Here, we describe associations between altered sensory processing evaluated from an electrophysiological perspective and its accompanying brain modifications revealed using different neuroimaging techniques.

16.2.1 Blood Flow and Oxygen Consumption: fMRI and PET

Cortical hyperresponsiveness in patients with migraine has several electrophysiological correlates, *deficient habituation* perhaps being the best described [5]. In healthy individuals, repeated sensory stimulation induces a progressive decrement in the magnitude of neuronal response [6]. This phenomenon, which was first observed in a species with a rather rudimentary nervous system [7], is known as habituation and is fundamental in the learning process as well as in protecting neurons against sensory overload. Remarkably, in patients with migraine, evidence has revealed that the normal habituation response is absent [8]; instead, cortical activations of persistent (or even increasing) amplitude to long-lasting sensory stimulation are observed [9]. This alteration has been attributed to enhanced cortical responsiveness, even if its innermost mechanisms remain partially unknown. Recently, a perhaps more explicit alternative in the evaluation of cortical excitability, namely *sensory gating ratio*, has been studied in migraine. In response to paired stimuli, the activation produced by the first stimulus is followed by an inhibitory-mediated suppression of the second response [10]. By evaluating the sensory gating ratio in a group of headache sufferers, investigators discriminated between patients with episodic migraine and patients with tension-type headache [11]. In addition, in another experiment, the results of sensory gating ratio evaluation helped investigators to identify underlying physiological alterations of the cerebral cortex that lead to chronic migraine [12]. Although concomitant electrophysiological and neuroimaging assessment of habituation or sensory gating has never been performed, findings of some imaging studies indirectly resemble the aforementioned neurophysiological observations. In 2010, Boulloche et al. conducted an H_2O^{15} PET experiment in which the protocol was specifically designed to facilitate habituation in healthy controls and thus accentuate differences in visual activation with respect to migraine patients, in whom habituation is impaired [13]. Following light stimulation at increasing levels of luminance, visual cortex activation was higher in patients with migraine than in healthy individuals and became even higher when a painful stimulus was simultaneously applied [13]. In an event-related fMRI study, Descamps et al. [14] described a lack of hemodynamic refractory effects to the second stimulus in a pair of stimuli separated by a short interstimulus interval in patients with migraine

without aura. These results were originally interpreted as the neurovascular correlate of deficient habituation, but are more in line with those of studies evaluating the sensory gating ratio. Possibly better associated with the electrophysiologically determined deficient habituation phenomenon was the fMRI study conducted by Stankewitz et al. in which responses to repeated trigemino-nociceptive and olfactory stimuli were evaluated. This study was pivotal not only because it directly revealed neuroimaging correlates of deficient habituation for the first time but also because it proved that habituation to olfactory stimuli, whose neural pathway has no thalamic relays, is not affected; in other words, it demonstrated that mechanisms behind deficient habituation most likely involve the thalamus [15].

16.2.2 Energy Metabolism: MRS and PET

One of the hypotheses concerning the underlying migraine pathophysiology suggests that migraine attacks are generated when metabolic demands at the cortical level are not fulfilled by metabolic offers [16], a scenario that is certainly capable of activating the alarm system of the brain (i.e., the trigeminovascular system; [17]). Enhanced sensory perception entails increased metabolic requirements, and sensory processing in patients with migraine appears to be particularly costly, metabolically speaking [18]. Rather than compensating for such alteration, available metabolic substrates in the brain of patients with migraine have repeatedly been found to be relatively reduced compared with those in healthy controls [19, 20]. Until now, these independent alterations (increased metabolic demands and reduced metabolic offers) have only been analyzed together in one study in which, to evaluate neurometabolic coupling in the visual cortex of patients with migraine, investigators calculated the ratio between visual evoked potential (VEP) amplitude (an electrophysiological response) and resting glucose uptake (calculated using PET, an imaging analysis) in specific areas of the occipital lobe. Results were in line with prior hypotheses: on a subject-by-subject basis, the ratio between metabolic requirements and metabolic offers in the cortex was approximately three times higher in patients with migraine than in healthy controls. This alteration might result in increased susceptibility to disruption of cortical homeostasis at times of increased metabolic demand, reduced metabolic offer, or both simultaneously [21]. Furthermore, one of the most interesting findings from that study, which strongly supports that electrophysiological tests largely benefit from being complemented by neuroimaging analyses, was that even patients with a relatively normal level of visual responsiveness are at risk of developing migraine if other factors that render them susceptible are present (in this case, reduced metabolic offers). For instance, increased visual responsiveness determined using solely electrophysiological techniques is observed in approximately 60 % of patients with migraine [22], but *relatively* increased cortical responsiveness with respect to metabolic reserves, identified through combining neurophysiological and neuroimaging analyses, is found in 90 % of patients with migraine [21]. Thus, the combination of electrophysiological and

neuroimaging tests increases our chances of understanding the underlying alterations that explain migraine pathophysiology.

16.2.3 Neurotransmitters Concentration: MRS

Magnetic resonance spectroscopy (MRS) allows one to noninvasively infer the concentrations of certain substances in the cerebral cortex on the basis of physical properties of their molecules. Using this method, numerous alterations have been described in groups of patients with migraine [20], with increased glutamate concentration particularly attracting researchers' attention. Glutamate is an excitatory neurotransmitter previously presumed to be involved in the enhanced sensory responsiveness of migraine [23]. In a recent high-field (7 T) MRS analysis, increased concentrations of glutamate levels in the visual cortex of patients with migraine without aura in the interictal period were observed [24]. This result was interpreted as the biochemical correlate of neuronal hyperexcitability in these subjects. Although appealing and perhaps mostly correct, according to the results of another experiment in which glutamate concentrations in the visual cortex and electrophysiological responses to visual stimulation were concomitantly measured in patients with migraine with aura, the assumption that glutamate is entirely responsible for hyperexcitability in migraine requires expansion. In the experiment in which neurophysiological and neuroimaging tests were combined, just as in previous studies, researchers found an increased glutamate concentration in the visual cortex of patients with migraine as well as a higher VEP amplitude compared with healthy subjects. However, modifications in glutamate concentrations induced by visual stimulation were not directly correlated with the magnitude of visually induced electrical responses [25]. In contrast to prior understanding, results from this experiment revealed that other neurotransmitters (other than glutamate) likely play a key role in migraine sensory hyperreactivity and that the underpinnings of such an alteration in patients with migraine are probably more complex than previously assumed. This would have never been revealed if both neurophysiological and neuroimaging tests were not concomitantly applied.

16.2.4 Brain Structure: MRI

Numerous studies have identified differences in brain structure between patients with migraine and healthy individuals [26]. Nonetheless, the association between electrophysiological responses and cerebral anatomy in patients with migraine remains somewhat unexplored. Although strong evidence indicates that specific regions of the visual cortex of patients with migraine are thicker than those of healthy controls [27], only one study jointly assessed the correlation between gray matter volume and visually evoked electrophysiological responses. In that study,

investigators recorded VEPs in groups of patients with migraine and then introduced these values into a volume-based morphometry analysis (an MRI-based technique) to search for brain regions where gray matter volume was correlated with the magnitude of visual responsiveness [28]. In addition, resting-state functional connectivity between distinct regions where voxels of gray matter were significantly correlated with the amplitude of visually evoked responses in patients with migraine was evaluated in an attempt to describe the functional interaction between these particular areas. By combining all these techniques, researchers were able to observe how visual hyperresponsiveness in migraine is the result of a multiareal process that largely involves attentional systems rather than a localized alteration of the visual cortex. Such a notion is in line with our current understanding of cerebral physiology [29] but would have never been determined if electrophysiological and neuroimaging techniques were not combined.

16.3 The Cyclic Nature of Migraine

Migraine is a cyclic disorder in which patients go through headache attack periods (i.e., ictal periods) separated by attack-free intervals (i.e., interictal periods). Attacks can last up to 3 days if untreated, and pain-free intervals usually comprise several days or weeks. These relatively short-term fluctuations are accompanied by dynamic brain changes that can be readily objectified using electrophysiological or neuroimaging techniques. With regard to electrophysiological responses, research has shown how brain responsivity becomes progressively more accentuated in the days that immediately precede an attack [30, 31] and then tends to normalize when the attack finally occurs [32, 33]. Functional neuroimaging correlates of these electrical variations were demonstrated in an elegantly designed fMRI study in which one patient was scanned daily for 30 days, allowing investigators to objectify the cyclic nature of migraine physiology from an imaging perspective and underline the critical role of the hypothalamic–brainstem interplay in attack generation [34]. From a structural point of view, a study conducted by Coppola et al. reported how morphometric changes involving critical diencephalic (e.g., thalamus) and cortical (e.g., parietal, temporal, and insular) regions previously linked with migraine pathophysiology also occur in the migraine cycle [35, 36]. Along with these short-term fluctuations, migraine severity may also vary over time in some patients, ranging between a low-frequency episodic form and a more debilitating form, namely chronic migraine. Researchers in the headache field have revealed some of the subjacent brain phenomena that occur in relation with migraine chronification. Using advanced MRI morphometry-based machine learning algorithms, a study accurately classified patients with episodic and chronic migraine, with results that reinforced the clinical classification system that had no previous empirical support [37]. Observing subtle structural alterations in the brains of patients with chronic migraine should not be surprising considering the prominent electrophysiological differences that have been formerly described. For example, in an MEG study,

Chen et al. [38] demonstrated how visual cortex excitability in chronic migraine strongly resembles a persistent ictal-like pattern and largely differs from that in episodic migraine. This experiment led to the notion that, from an electrophysiological perspective, chronic migraine may be conceived as a never-ending headache attack [39]. In line with this concept, similar alterations were observed in high-frequency oscillations elicited by somatosensory stimulation in patients with episodic migraine recorded in the ictal period as well as in patients with chronic migraine [40]. Nonetheless, although similar from an electrophysiological perspective, patients actively experiencing a headache seem to have a specific signature that distinguishes them from patients with chronic migraine. This distinction was reported in an fMRI study in which investigators found a small region in the posterior hypothalamus that was more activated by painful ammonia stimulation during headaches, regardless of the migraine subtype (i.e., episodic or chronic migraine; [41]). Experiments simultaneously analyzing the cyclic nature of migraine from both electrophysiological and neuroimaging perspectives are definitively warranted.

16.4 Migraine Aura

Migraine aura is a transient neurological symptom that usually precedes a migraine attack. The most widely accepted cortical phenomenon that explains the clinical features of migraine aura is cortical spreading depression [42]. Cortical spreading depression is a propagating wave of neuronal and glial depolarization (identified as a depression of electroencephalographic activity) that induces changes in local cerebral perfusion. It was originally described in rabbits by Aristides Leão, a Brazilian physiologist, in 1944 [43, 44]. Despite its early theoretical proposition as the electrophysiological correlate of migraine aura [45, 46], experimental evidence of cortical spreading depression in patients experiencing aura symptoms was only obtained almost 40 years after the idea was proposed. The first of such publications was actually not from the electrophysiological but from the neuroimaging field and analyzed progressive changes in cortical perfusion (a surrogate marker of cortical spreading depression) instead of neuronal activity [47, 48]. These results were later corroborated by other experiments in which more refined neuroimaging techniques were used [49, 50]. Direct evidence supporting cortical spreading depression expressed as a propagating alteration of cerebral electric or magnetic activity in patients during migraine aura is, to date, limited. Two MEG studies [51, 52] and one case report [53], together with one EEG experiment [54], constitute all electrophysiological evidence that is available. Concomitantly evaluating the electrophysiological alterations of migraine aura together with its accompanying modifications in cerebral blood flow in a combined EEG–fMRI analysis would be of interest. This would certainly allow for a better understanding of this intriguing phenomenon, but until such experiments are carried out, hypotheses and assumptions will prevail.

16.5 Conclusion

In this chapter, we analyzed the basics of electrophysiological experiments that have enhanced our comprehension of migraine pathophysiology and their neuroimaging correlates. We have observed how consistency between electrophysiological and neuroimaging outcomes leads to a more comprehensive and refined understanding of the migraine brain and discrepancy tends to result in new, strong, and evidence-supported hypotheses. Combining direct analysis of neural activity through electrophysiological techniques with the complex evaluation of accompanying brain phenomena through neuroimaging studies entails so many advantages that it should be strongly encouraged in the future.

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Chapter 17
Neurophysiological Model of Migraine Pathophysiology: Bringing the Past into the Future

Gianluca Coppola, Francesco Pierelli, Jean Schoenen, Shuu-Jiun Wang, and Wei-Ta Chen

Abbreviations

ACh	Acetylcholine
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CNV	Contingent negative variation
CSD	Cortical spreading depression
EEG	Electroencephalography
EP	Evoked potential
mDNA	Mithochondrial DNA
nDNA	Nuclear DNA
PAG	Periaqueductal grey matter
PET	Positron emission tomography
rTMS	Repetitive transcranial magnetic stimulation
SSRIs, SNRIs	Serotonin and serotonin-norepinephrine reuptake inhibitors

G. Coppola (✉) · F. Pierelli
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy
e-mail: gianluca.coppola@uniroma1.it

J. Schoenen
Headache Research Unit, University Department of Neurology CHR, Citadelle Hospital, University of Liège, Liège, Belgium
e-mail: jschoenen@uliege.be

S.-J. Wang · W.-T. Chen
Brain Research Center, National Yang-Ming University, Taipei, Taiwan

School of Medicine, National Yang-Ming University, Taipei, Taiwan

Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

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tDCS	Transcranial direct current stimulation
TRPA1	Transient receptor potential ankyrin 1
TVS	Trigeminovascular system (TVS)

17.1 Introduction

The definition of a migraine attack as 'nerve-storms' made by Liveing [1] is perhaps, as also pointed out by Oliver Sacks [2], the best metaphor to describe the sequence of symptoms starting 24–48 h before and lasting up to 24 h after the aura and headache phases, which characterizes the overt manifestation of the migraine syndrome. Migraine is indeed a complex of symptoms that can be triggered by diverse factors, amongst which are alcoholic beverages, stress, sleep disturbances and weather conditions [3] including lightning storms [4]. Such triggers are not causes, however, because for a factor to be possibly causal, it must be present also outside of an attack as a predisposing factor.

Genes could cause the fertile ground that predisposes to the recurrence of migraine attacks. The 'holy grail' of migraine genetics has not yet been found, however, probably because the migraine predisposition is not linked to a single gene, but to multiple genetic peculiarities that, taken individually, cause subtle non-pathogenic anomalies, but perturb the brain's equilibrium allowing triggers to ignite an attack, when they occur in combination [5]. Although mutations of single genes are not found in the common forms of migraine, contrary to familial hemiplegic migraines, it is well known that migraine runs in the family with a predominant maternal transmission.

Neurophysiology had the primacy of unraveling for the first time that in migraine the brain has peculiar functional characteristics even between attacks, i.e. when the patient is completely, or almost completely, asymptomatic.

In this book several chapters illustrate how the migraine brain has been explored with virtually all hitherto available neurophysiological methods. Various functional abnormalities were detected not only at the cortical level, as the general clinical hypersensitivity of the migraine could suggest, but also, albeit subtle, at the spinal (Perrotta, Chap. 8; Vollono, Chap. 7; Uglem, Chap. 11), brainstem (Vollono, Chap. 7) and thalamic and thalamocortical levels (Coppola and Pierelli, Chap. 6).

The first conclusion emerging from these studies is, therefore, that there is a global dysfunction of sensory information processing in the nervous system of migraine patients for all sensory modalities, except for the olfactory one (Chen et al., Chap. 2; Coppola and Magis, Chap. 3).

The second neurophysiological hallmark is that most of these abnormalities are reversible, as they are evident outside of a migraine attack, but either improve or sometimes worsen just before, i.e. during the premonitory phase, or during an attack (Sand et al., Chap. 1; Coppola and Magis, Chap. 3, Chen et al., Chap. 2; Coppola

and Pierelli, Chap. 6), possibly accompanied by abnormal sensorimotor integration (Boran et al., Chap. 9). Pharmacological therapies can often contribute to the normalization of cortical activities.

The third distinguishing feature of migraine is that neurophysiological responses are in part different when evoked by noxious or innocuous stimuli, likely because of a central sensitization in pain processing (Coppola and Magis, Chap. 3; de Tommaso et al., Chap. 10). Whether or not these alterations are due to a general deficit in pain inhibition by the endogenous pain control systems both at spinal and brainstem (Vollono, Chap. 7; Perrotta, Chap. 8) and frontal levels (de Tommaso et al., Chap. 10) remains to be determined [6]. Further studies are necessary to determine the causal link between the functional abnormalities during wakefulness and the alterations in quality and structure of sleep detected with polysomnography (Engstrøm and Rains, Chap. 5).

Fourth, although it is commonly postulated that the migraine aura is caused by cortical spreading depression, there is to date only indirect evidence in favor of this phenomenon from neuroimaging and, partly, from neurophysiological studies (Ambrosini and Coppola, Chap. 14).

Fifth, the abnormalities in information processing of painful or innocuous stimuli found in adult migraineurs can also be found in adolescents and even in subjects defined as being 'at risk for migraine' because they are born from parents affected by migraine and hence probably carry a higher genetic load (Coppola et al., Chap. 12; Valeriani and Gazerani, Chap. 15).

Sixth, the recurrence of cephalic pain is associated with cognitive disturbances and leads to behavioural, often ineffective, strategies to avoid pain, which is reflected in abnormalities of neurophysiological responses to cognitive tasks (Mickleborough et al., Chap. 4). In fact, various cognitive dysfunctions have been described in the various phases of the migraine cycle [7–13] and worsen when migraine becomes chronic [14–16].

Seventh, it seems obvious, but cannot be taken for granted, that all these functional alterations can determine transient or lasting plastic changes at the synaptic level (Coppola and Antal, Chap. 13). This can be responsible for changes in synchrony of temporal activation and in functional dynamic connectivity between brain areas and for their modification by sensory stimuli (Sand et al., Chap. 1; Chen et al., Chap. 2; Coppola and Magis, Chap. 3; de Tommaso et al., Chap. 10). These plastic synaptic modifications may be at the basis of the micro- and macro-structural changes of cerebral white and grey matter that have been identified since several years with modern neuroimaging techniques [6].

Eighth, we have only recently gained some insight in the neuroanatomical correlates of the various ictal and interictal dysfunctions, evidenced by neurophysiology. Several recent studies show how the cerebral hyperresponsiveness observed with evoked potentials in migraine is associated with macro-structural changes, abnormal functional connectivity or a mismatch between the increased neural activity and brain energy availability in patients between attacks (Lisicki and Chen, Chap. 16).

17.2 Neurophysiological Model of Migraine Pathophysiology

As evidenced by the numerous neurophysiological studies performed over the migraine cycle, migraine is not a static brain disorder, but instead a disorder with a protean pathophysiological signature that changes depending on the phase of its cycle. It involves the nervous system in many ways and at various sites (see Fig. 17.1).

In a neurophysiological model of migraine pathophysiology, genetic predisposition, due to peculiarities in nuclear (nDNA) and/or mitochondrial (mDNA) DNA, has a pivotal role. As mentioned before, asymptomatic 'at-risk' subjects have the same neurophysiological pattern as interictal migraineurs [17–19]. Moreover, the neurophysiological responses of parents correlate closely with those of their children [20]. In chronic migraine, there is a close relationship between genetic polymorphisms, neurophysiological patterns and acute medication overuse [21, 22]. Unlike in familial hemiplegic migraine, the genetic basis of the aura in the common forms of migraine aura remains elusive; the neurobiological link between the aura and activation of the trigeminovascular system also remains speculative in humans. Interestingly, visually induced electrical and biochemical brain responses as well as neuromuscular junction safety factor differ between patients with strictly visual auras and those with complex neurological auras [23–26].

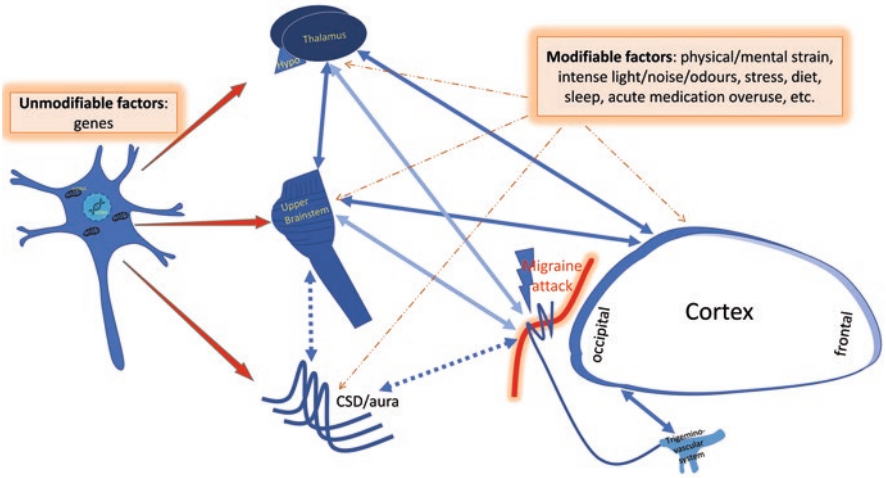

Fig. 17.1 Schematic representation of the pathophysiological model of migraine developed according to the data provided by neurophysiological studies. The figure shows the areas of the nervous system involved, their link (with a continuous line when evident, with a dotted line when only hypothesized) to form a cybernetic system. In the figure are also represented some of the possible non-modifiable and modifiable factors able to disrupt the system and determine the activation of the cerebral visceral alarm system par excellence, the trigeminal-vascular system. The final product is the triggering of a migraine attack, which tries to rebalance the system. In chronic migraine this system never stops being re-balanced because the TVS is always active (daily headache) and reinforced by the central sensitization process. See the text for more explanations

The proteins certain genes code for set the level of excitability of different brain structures. In migraineurs, for instance, they may influence the propensity to develop peripheral and/or central sensitization, they may reduce the efficiency of pain control systems from the frontal lobes to the upper brainstem, or more generally, they may alter the synaptic hyperpolarization/depolarization activity that underlies neuronal plasticity, i.e. learning and memory functions. These are precisely functions that are altered in migraine, such as habituation to sensory stimuli and short- and long-term adaptation processes induced by non-invasive transcranial brain stimulation. The studies analysing high-frequency EEG/EP oscillations indicate that thalamic activation of sensory cortices is abnormal in migraine and thalamocortical afferents are known to be under the tonic control of the brainstem and limbic system. This type of functional alteration is called 'thalamocortical dysrhythmia', which is likely to be responsible for the general hyperresponsiveness of the migraine brain [27].

Unfortunately, clinical neurophysiology methods have provided little information on another diencephalic structure, the hypothalamus, that has received renewed attention during the last 5 years [28]. Modern neuroimaging studies support indeed with reasonable certainty the historical view [29] of the hypothalamus as a cerebral structure playing a crucial role in the periodicity of migraine attacks, its anterior part being more active up to 48 h before an attack during the pre-ictal phase when premonitory symptoms may occur [28, 30, 31]. An abnormal activation of the anterior hypothalamus also appears to be present during chronic migraine [32–34], confirming that chronic migraine could be considered, brain activity-wise, as a never-ending attack [35]. The hypothalamus is anatomically connected to the two most important pain control areas, the one located in the frontal lobes [36] and the one located in the midbrain [28, 37], and therefore has antinociceptive functions [38]. In addition, the neuroendocrine (orexinergic and non-orexinergic) hypothalamic system that is critically involved in coordinating appropriate physiological and behavioural responses to aversive and threatening stimuli [39, 40] like headache may be involved in this pathophysiological model. We speculate that the hypothalamus, together with the trigeminovascular system (TVS), the major alarm system of brain viscera, forms an important neural system designed to maintain brain homoeostasis by regulating homoeostatic needs, such as energy balance, osmoregulation and emotional response [41]. Whether the visual cortex that is also activated preictally in most imaging studies [28, 30, 31] and both directly or indirectly connected with the hypothalamus has a primary or secondary role in initiation of the migraine attack remains to be determined.

The high level of cortical responsivity between attacks of migraine is extremely energy-consuming for the brain [42]. A combined interictal study of VEP and FDG-PET has shown that in the visual cortex of migraineurs neuronal activation by far exceeds glucose uptake, and thus metabolic supply, during visual stimulation [43]. A mismatch between cerebral energy demands and energy reserve can lead to a critical disequilibrium able to activate the hypothalamo-TVS homoeostatic system and to ignite the migraine attack [42]. In a cybernetic system, like the human brain, the ignition of this system, whilst generating the headache and associated symptoms

of an attack, can be considered as the only means to bring the brain back into balance, i.e. to avoid 'rupture' of cerebral homoeostasis. In chronic migraine, this hypothalamo-TVS system in a certain way 'never stops' being active [35]. This is likely favoured by unmodifiable factors, such as the genotypes mentioned above, and persisting, though modifiable, factors, such as behavioural alterations like overuse of symptomatic drugs and biorhythm imbalances, for example, due to insufficient physical activity, forced rupture of circadian rhythms or inadequate dietary habits. All these factors are likely to contribute to an increase in oxidative stress, promote a persistent pro-inflammatory state and alter basal metabolism [44], all contributing in an additive way to unbalance the cerebral cybernetic system and thus increase the propensity for activation of the hypothalamo-TVS system.

17.3 Possible Therapeutic Interventions Based on Neurophysiological Evidence

Various targets for therapeutic intervention in this construct of migraine pathogenesis are schematized in Fig. 17.2.

As mentioned above, migraine affects the nervous system at multiple levels, from the first sensory division of the trigeminal nerve to the cortex, through the brainstem aminergic nuclei (raphe, locus coeruleus), diencephalon, basal forebrain (nucleus basalis) and periaqueductal grey matter (PAG). The subcortical structures seem to play a key role both in the interictal cortical hyperresponsive sensory processing and in attack generation. Not only the brainstem structures but also the diencephalon, hypothalamus and thalamus are actively involved in preparing and starting the migraine attack [31]. Therefore, drugs acting at these CNS sites might mitigate both attacks and subcortico-cortical neurophysiological abnormalities.

There is convincing evidence from neurophysiological and functional imaging studies that central nervous system changes precede the activation of the TVS. Although the pain is most likely generated in the peripheral portion of the TVS, notable via the release of calcitonin gene-related peptide (CGRP) in meningeal sensory afferents [45], neurophysiological signs of peripheral trigeminal sensitization between attacks are scarce and subtle, whilst there is robust evidence of central sensitization (Uglem, Chap. 11). Because of their high molecular weight, the novel anti-migraine monoclonal antibodies blocking CGRP transmission act in principle exclusively in the peripheral portion of the TVS, and yet they have a prophylactic effect. It is of interest in future neurophysiological studies to verify if they exert a pure peripheral effect or are also able to modify central areas involved in migraine pathophysiology, such as the hypothalamus or periventricular organs where the blood-brain barrier is lacking. If the former is the case, the monoclonal CGRP/rec mAbs may act as a long-lasting attack treatment rather than as a genuine preventive treatment supposed to mitigate the interictal central nervous system dysfunctions that may lead to a migraine attack.

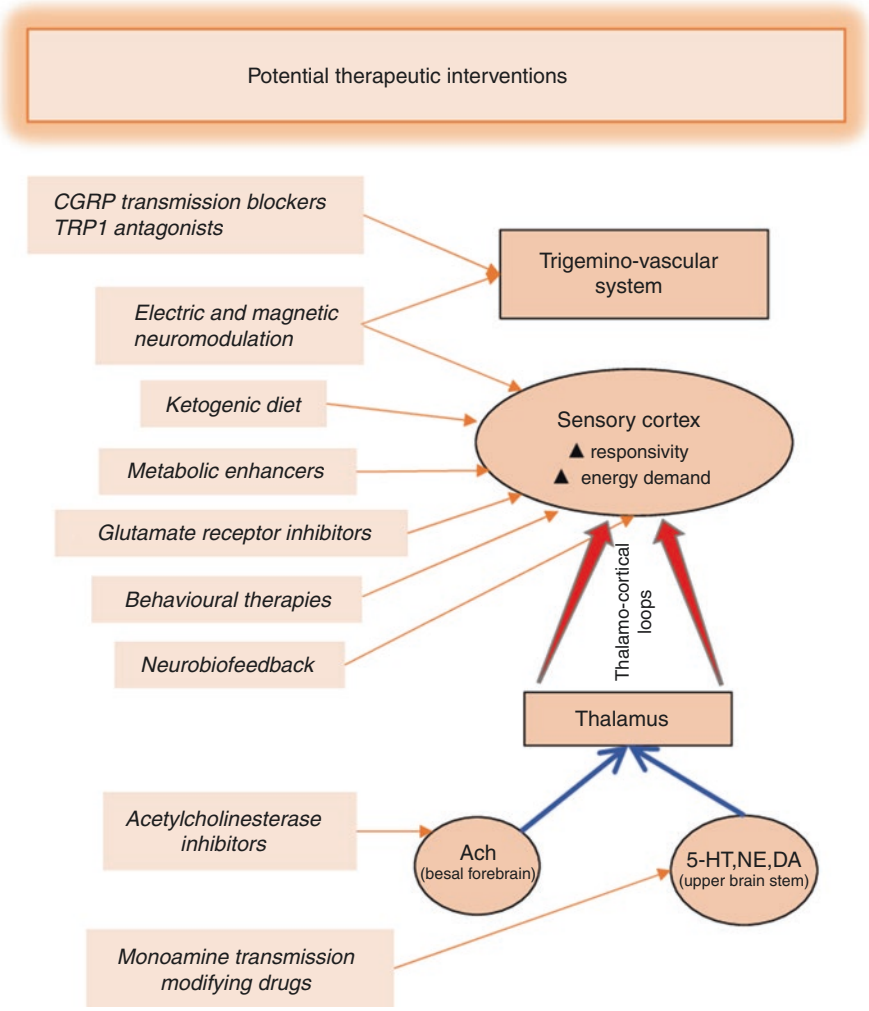

Fig. 17.2 Schematic representation of the brainstem-thalamocortical network and trigeminovascular system thought to be relevant for migraine pathogenesis and the potential therapeutic interventions

A disturbance of the serotonin metabolism has been described in migraine patients [46]. The efficacy of the serotonin transmission-modifying drugs in both the acute and prophylactic treatment of migraine is well accepted.

Amongst the monoamine reuptake inhibitors, a pharmacological class used in migraine prophylaxis, the tricyclic agent amitriptyline is the only with some evidence for efficacy. By contrast, the selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs, SNRIs) have not been found to be consistently effective in migraine, but available information is too scarce to allow any definitive

conclusion. Nevertheless, these agents were shown to have specific effects on cortical responsivity [47, 48], suggesting that more studies in migraine prophylaxis may be worthwhile [49].

Interactions between serotonin and other monoamines, such as acetylcholine, have been described in animal models [50–52], indicating that the serotonergic system could be only one of the possible targets for migraine treatment. As a matter of fact, thalamocortical projections supposed to be dysfunctioning in migraine (Coppola and Pierelli, Chap. 6) are chiefly cholinergic, and in neurophysiological studies acetylcholine (ACh) can influence cortical responsivity in animals [53, 54] and in humans as far as thalamocortical activity [55] or cortical inhibitory functions are concerned [56]. Interestingly, in animals, ACh significantly increases firing in nociceptive afferents of meningeal trigeminal nerves [57] whilst muscarinic receptor activation decreases overall the excitatory/inhibitory ratio and inhibits both initiation and propagation of cortical spreading depression [58]. Nicolodi et al. found in an open-label proof-of-concept study that a 2-month treatment with donepezil, a second-generation acetylcholinesterase inhibitor, reduced the frequency of migraine attacks, cumulative hours with headache and pain severity; its efficacy was superior to that of propranolol [59]. Acetylcholinesterase inhibitors could contribute to stabilize the aminergic innervation of the thalamus and cortex and to inhibit cortical spreading depression. Placebo-controlled trials of acetylcholinesterase inhibitors in migraine prevention are thus worthwhile.

Many neurophysiological [60, 61] and neuroimaging [62–64] studies suggest that the glutamatergic neurotransmission is abnormal in migraine. Genes that are involved in glutamate signaling may be implicated in migraine [65]. Glutamate receptor inhibitors possess antinociceptive properties in animal models of trigeminovascular nociception [66] and hence are promising drugs for acute migraine treatment [67]. There is some evidence in favour of an association between certain glutamate receptor polymorphisms and somatosensory evoked responses in chronic migraine with medication overuse headache [22].

Another path to explore is the metabolic facet of migraine pathophysiology. MR spectroscopy, PET scan and blood studies of glucose and insulin metabolism have established that the mitochondrial energy metabolism is altered in the brain of migraine patients between attacks [68]. This is supported by therapeutic trials of so-called metabolic enhancers (nutraceuticals) acting on the respiratory chain [69] and of ketogenic diet [70]. The latter, besides enhancing mitochondrial metabolism, is able to modulate cortical excitability, as illustrated by the normalization of visual and somatosensory evoked potentials in episodic migraine patients after 1 month of ketogenic diet [71, 72]. Further studies are necessary to determine if the neurophysiological patterns can predict the therapeutic response and if the normalization of cortical evoked responses is due to an enhancement of inhibitory circuits or a reduction in excitatory activity, or to an effect on both.

As mentioned above, external trigger factors likely contribute to an increase in oxidative stress that may promote a persistent pro-inflammatory state and alter the basal energetic metabolism of the migrainous brain [44, 68]. Sensory neurons of the trigeminal nerve express transient receptor potential ankyrin 1 (TRPA1)

cation channels, which are of particular interest in migraine since they sense a large series of reactive by-products of oxidative stress and seem to contribute to the transition from an acute to a chronic pain condition [73]. TRPA1 activators can trigger migraine attacks and analgesic and specific anti-migraine drugs are able to inhibit or desensitize TRPA1 channels. Novel TRPA1 antagonists may represent a new class of drugs to mitigate the oxidative stress response and to treat migraine [74].

For clinical practice, it is of interest that non-pharmacological strategies are able to modulate cortical pre-activation levels and excitability and can be useful in migraine prophylaxis. Contingent negative variation (CNV) biofeedback, a psychophysiological intervention, was effective in treating migrainous children [75]. Although the effect could be related to other factors than the self-regulation, it suggests that further therapeutic trials of neurofeedback are worthwhile in migraine, including adult migraineurs.

Other means to modify activity and metabolism of cortical neurons are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), both of which can induce long-lasting modifications of cortical excitability. These neuromodulatory methods have shown promising results in treating major depression [76, 77]. Unfortunately, despite the great interest in these methods, the results obtained so far in the acute or preventive treatment of migraine are scarce and partly contradictory [78]. Peripheral nerve neurostimulation such as cervical vagus nerve stimulation or external trigeminal neurostimulation can also be effective as adjunctive therapies in migraine [79]. Further studies are needed to determine whether these non-invasive neurostimulation methods are more effective if they are selected and adapted according to the interictal peripheral and cortical neurophysiological profile of migraine patients, as demonstrated in a proof-of-concept study [80] and in other functional brain disorders [81].

17.4 Perspectives on Neurophysiology in Migraine

More than 3000 years passed since the first description by Hippocrates of migraine as a periodic syndrome encompassing aura, hemicranial pain and associated gastrointestinal symptoms: ‘he seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck....vomiting, when it became possible, was able to divert the pain and render it more moderate’ [82]. But only about 150 years have passed since the first recognition of migraine as a paroxysmal brain disorder by Liveing: ‘A form of centrencephalic seizure, the activity of which is projected rostrally upon the cerebral hemi-spheres, and peripherally via the autonomic nervous system’ [29].

The temporal resolution of modern neurophysiological techniques, in combination with the high spatial resolution of modern MRI techniques, has enabled

neuroscientists to make giant strides in understanding the pathophysiology of migraine. Given the progress made since 1959, when Golla and Winter [83] used old-fashioned four-channel EEG to study the brain in migraine, the time is ripe for substantial advances in disentangling its multiple pathophysiological facets. Progress in the next few years will largely depend on a better understanding of the mechanisms underlying cortical hyperresponsivity in migraineurs, of the underpinnings of its variations over the migraine cycle and of its relation with brainstem-thalamocortical rhythms and activity of subcortico-(thalamo-)cortical aminergic pathways. It will also be necessary to disentangle the link between the fluctuations in cortical responsivity and the activation of the hypothalamo-TVS pathway, as well as the link between the latter and the migraine aura. It is of uttermost importance to gather more data on the geno-phenotype correlations in the various migraine forms. Moreover, since migraine has many comorbidities, ranging from psychiatric to chronic pain disorders, it is of fundamental importance to acquire more information on possible electrophysiological links with the various comorbid disorders, jointly with a better clinical characterization of patients. Finally, the link between metabolic factors, cortical spreading depression and TVS activation needs to be clarified, in particular with regard to the possible role of the oxygen/ATP sensing system, involving hypoxia-inducible factor (HIF), and to the role of metalloproteinases able to break down the blood-brain barrier and to allow brain-derived factors accessing the TVS system.

To conclude, given the multiple anatomical and functional peculiarities found in the brain of migraine patients even between attacks, we think it is time to move from the original definition of migraine as ‘non-organic central pain’ by Federigo Sicuteri [84] to that of ‘biobehavioural organic maladaptive central pain’, which incorporates the biological and behavioural aspects of the disorder, as well as the accompanying morpho-functional plastic alterations.

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