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Electrophysiological findings in migraine may reflect abnormal synaptic plasticity mechanisms: A narrative review

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Abstract

Background: The cyclical brain disorder of sensory processing accompanying migraine phases lacks an explanatory unified theory.

Methods: We searched Pubmed for non-invasive neurophysiological studies on migraine and related conditions using transcranial magnetic stimulation, electroencephalography, visual and somatosensory evoked potentials. We summarized the literature, reviewed methods, and proposed a unified theory for the pathophysiology of electrophysiological abnormalities underlying migraine recurrence.

Results: All electrophysiological modalities have determined specific changes in brain dynamics across the different phases of the migraine cycle. Transcranial magnetic stimulation studies show unbalanced recruitment of inhibitory and excitatory circuits, more consistently in aura, which ultimately results in a substantially distorted response to neuromodulation protocols. Electroencephalography investigations highlight a steady pattern of reduced alpha and increased slow rhythms, largely located in posterior brain regions, which tends to normalize closer to the attacks. Finally, non-painful evoked potentials suggest dysfunctions in habituation mechanisms of sensory cortices that revert during ictal phases.

Conclusion: Electrophysiology shows dynamic and recurrent functional alterations within the brainstem-thalamus-cortex loop varies continuously and recurrently in migraineurs. Given the central role of these structures in the selection, elaboration, and learning of sensory information, these functional alterations suggest chronic, probably genetically determined dysfunctions of the synaptic short- and long-term learning mechanisms.

Keywords

Aura, transcranial magnetic stimulation, electrophysiology, cortical excitability, synaptic plasticity, neurophysiology

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Introduction

Migraine is one of the most common neurological disorders, affecting over one billion people worldwide. As a severe condition that typically affects young individuals, it also represents a leading cause of disability (1). Even though the origin of migraine is still not completely understood, it is widely considered to represent a cyclical brain disorder of sensory processing, influenced by a complex combination of genetic, behavioural and environmental factors (2). For example, migraine attacks can be triggered by a wide

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number of factors, such as physical or psychological stress, skipping a meal, loss or increase in sleep, and hormonal changes. The lack of a clear genetic inheritance accounts for the variability in clinical presentation of the disease, which in turn translates into an equally wide variability in the response to prophylactic treatments. This complex pathophysiological puzzle is one of the reasons why migraine has historically been considered as the functional brain disorder *par excellence*. In this context, non-invasive electrofunctional techniques used to investigate brain processing systems and neuronal excitability have greatly contributed to a better understanding of the biology of migraine disorder (3).

Among the array of available techniques, transcranial magnetic stimulation (TMS), electroencephalography (EEG), as well as evoked potentials (EPs) – particularly visual and somatosensory evoked potentials (VEPs and SSEPs, respectively) – have been used abundantly for the investigation of migraine (4). Although these tests do not allow for individualized clinical analyses, they nonetheless represent flexible instruments for analysing the neurobiology of headache disorders. In some cases, neurophysiological tools have even evolved into treatment strategies for migraine, as is the case for TMS (5,6), which has a direct effect on cortical spreading depression (CSD), thalamic neural modulation and cortical GABAergic circuits (7,8).

In this article we will first proceed to summarize and describe the main studies that have applied TMS, EEG and EPs for the investigation of cortical brain responses in migraine, migraine with aura, and associated conditions such as visual snow syndrome (9). We will focus on the different techniques and methodologies, highlighting how, overall, the results found in the literature can be directly related to an alteration of the mechanisms underlying synaptic plasticity and cortical information processing.

Methods

This is a narrative review on the use neurophysiological investigations in migraine and related disorders. A literature search was conducted on PubMed (by authors FP, AV and GS independently) on 15 October 2022 and repeated on 16 February 2023. We searched for original research publications on studies using either TMS, EEG, SSEPs or VEPs to investigate migraine with and without aura and visual snow, using the following terms: "TMS OR transcranial magnetic stimulation", "EEG OR electroencephalography", "VEP OR visual evoked potentials", "SSEP OR somatosensory evoked potentials" AND "migraine", "aura OR migraine with aura", "visual snow OR visual snow syndrome". Additionally, we selected manuscripts known to the authors, as well as a book chapter written by author GC (10). The final selected articles were revised by all authors. We summarized the key methods and results for each technique in a narrative way in the text and in Figure 1.

Neuromodulatory techniques and cortical plasticity in migraine

The first neuromodulatory technique originated in the 1980s from the development of the TMS procedure, a tool used to investigate the integrity of corticospinal motor pathways in humans via a magnetic field capable of electrically charging the underlying cortex in a non-invasive manner (11). Over the last few decades different stimulation paradigms using TMS, but also using transcranial direct current stimulation (tDCS), have been developed, allowing to measure neurophysiological functions and to induce transient or durable changes of cortical excitability and neuronal circuitry *in vivo*. These include single-pulse TMS (sTMS), repetitive (r)TMS, tDCS, and more recently integration with functional neuroimaging and electroencephalography (TMS/EEG) (12). These techniques use a mechanism akin to the short- and long-term depression (STD, LTD) or potentiation (STP, LTP) seen at the synaptic level to either decrease or enhance the degree of excitability of the underlying cortex. Depending on the stimulation paradigm this can be achieved temporarily or in a sustained manner. Differences can also depend on the stimulus location; most TMS studies in migraine have focused on stimulating either the motor or occipital cortex, or both.

Motor and occipital cortex stimulation

TMS over the primary motor cortex can objectively measure corticospinal excitability by measuring the resting motor threshold (RMT). RMT, together with amplitudes of motor evoked potentials (MEPs), represent the most basic measure of motor cortex excitability (13) with lower thresholds and larger amplitudes suggesting increased cortical excitation, and vice versa. Migraine RMTs were found to be normal (14–18), reduced (19) or increased (20,21). These contradictory results could be explained by the fact that, during the interictal phase of migraine, the RMT value fluctuates based on the number of days since the last attack (22). The cortical silent period (CSP), characterized by electromyography (EMG) silence after a single TMS pulse over contralateral M1 (23), is widely used to measure intracortical and interhemispheric inhibitory processes (24). Several studies showed a shortened CSP in migraine patients, i.e. a defective inhibition (19,25–29). Other studies, however, including patients with aura

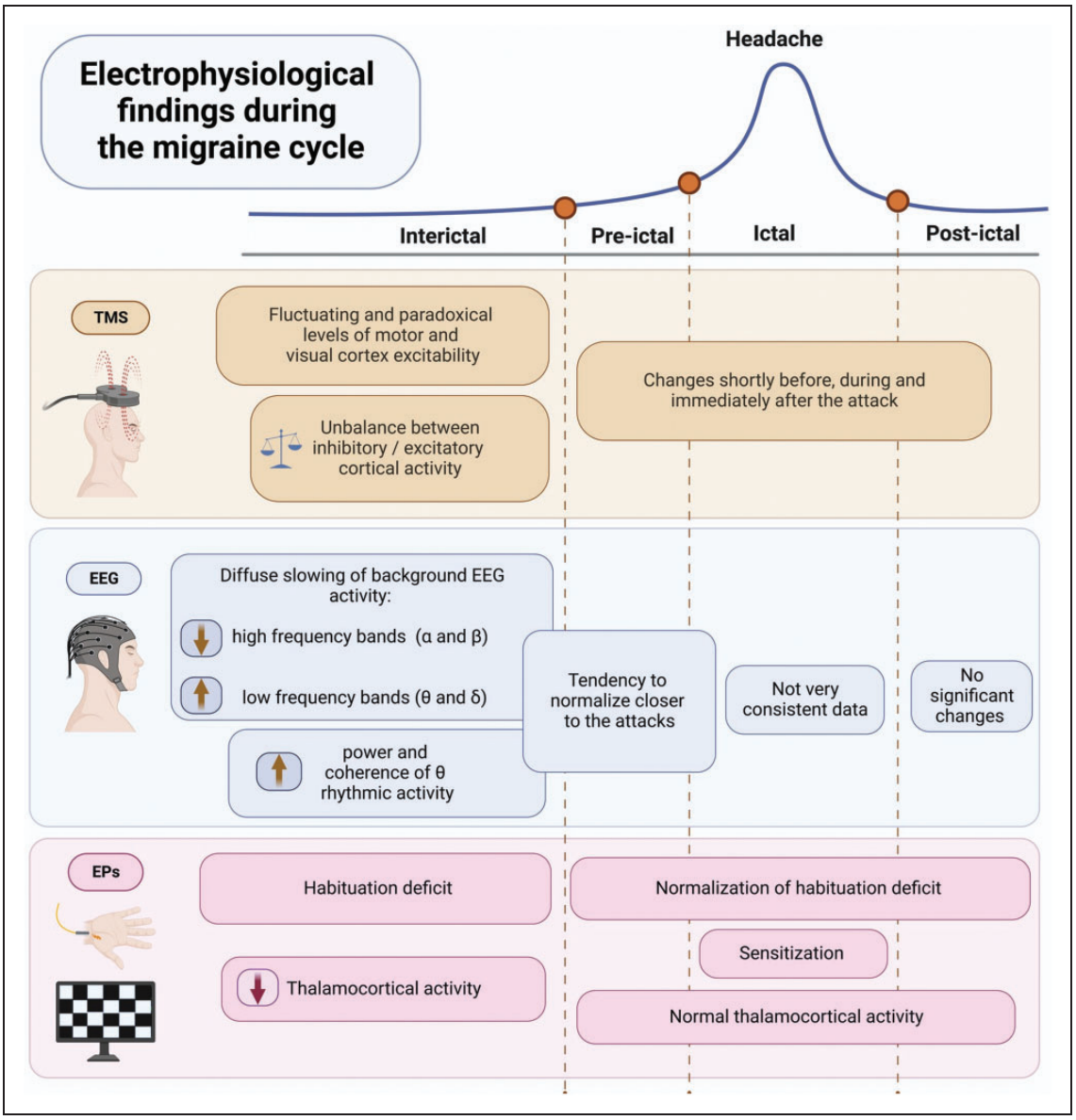

Figure 1. Main electrophysiological changes found in migraine using TMS, EEG, SSEPs and VEPs, according to the different phases of the migraine cycle. Created with BioRender.com.

(16), familial hemiplegic migraine (30) or pediatric patients (31), failed to detect any abnormalities in the CSP (32–35).

Phosphene thresholds (PTs) measure occipital cortex excitability by determining the minimum intensity of TMS stimulation over the visual cortex that induces phosphenes. PTs only use patient reports and are thus less objective than RMTs.

As with RMT measurements, PT levels in migraine have been variable. Some studies found decreased levels of PT, suggesting cortical hyperexcitability (16,19,31,36,37), while others found equal (15,32,38) or even increased (39) levels in patients compared to healthy controls. While contrasting results emerged from studying patients with migraine without aura, consistent results came from the investigation of migraine with aura patients. Indeed, in migraine with aura most of the studies have found increased visual cortex excitability, as shown by lower PT values, higher phosphene generation (36,40), and paradoxical facilitatory responses to excitatory stimulations (41,42), with one exception (32).

Abnormal mechanisms of cortical plasticity

Repetitive stimulations of TMS over the same scalp site (rTMS) are known to alter cortical excitability and inhibitory circuits, and could be used to study cortical responsivity to these changes. Depending on frequency

of stimulation, rTMS has the ability of altering neuronal plasticity by either inhibiting (at low frequencies, 1 Hz) (43) or activating (at high frequencies, 5–10 Hz) the underlying cortex (44). First observed by Bohotin et al. (15), high-frequency rTMS can normalize the interictal habituation deficit of VEPs by increasing cortical excitability when administered to the visual cortex. However, the researchers found no changes in habituation when they used low-frequency rTMS to reduce cortical excitability. In healthy subjects, instead, excitatory stimulation had no effect, while inhibitory stimulation induced a habituation deficit resembling that seen in migraine patients. The authors came to the conclusion that the migraine brain is inherently hypoexcitable throughout the intercritical period, although this interpretation is questioned by others based on data collected using different experimental settings (42,45). rTMS was also applied to the sensorimotor region, and the initial amplitude and delayed habituation of SSEPs were recorded (46,47). It is interesting to note that excitatory rTMS normalizes SSEPs in migraine patients by increasing thalamocortical activity, which is instead decreased at rest. By increasing cortical activity with anodal tDCS on the visual (48) and temporal (49) cortices, normalization of cortical evoked responses can also be accomplished. Additionally, migraineurs show a lesser ability than healthy subjects to modify cortical responses over the long term following daily rTMS sessions (50). There are further paradoxical effects reported after cortical inhibitory neuromodulation, which in migraine sufferers decreases the threshold of phosphenes (41,42) and increases the amplitude of motor potentials (51), as opposed to healthy subjects. These changes in migraine can be explained by a malfunction in the STD and LTD mechanisms, which are plasticity phenomena that occur in the firing synapse and depend on changes in synaptic weights or in the number of receptors expressed in the synaptic cleft as a function of learning and memory (52).

Using psychophysiological methods, evidence of LTD processes failure in the migraine brain has also been shown. Migraine patients with aura appear less susceptible to the suppression of perceived accuracy caused by TMS than migraine sufferers without aura and healthy individuals (37,53–57). The same is true when applying metacontrast masking, which involves the effect of masking a picture, such as a ring, after presenting a letter (58–60). In a different study of psychophysiology, the authors used the sound-induced flash illusion paradigm to describe anomalies in multisensory integration. In particular, during an attack, the feeling of numerous flashes was diminished or eliminated in patients with migraine with aura (61), and patients did not experience short-term depression after receiving inhibitory tDCS (62). Regarding VEPs, phosphenes, and MEPs, the same absence of inhibitory tDCS neuromodulation was seen (41,42,63). This could imply either that baseline suppression cannot be further suppressed, or that LTD mechanisms are essentially dysfunctional and unmodulable.

However, instead of observing a physiological rise, several researchers who attempted to explore the processes of STP through suprathreshold trains of high-frequency (5 Hz) rTMS noticed a drop of MEP amplitudes along the train of stimuli (64,65). These paradoxical neuromodulatory responses are superpotentiated during the preictal phase, whereas they are conversely depressed during an attack and shortly after a pain-free period, depending on the point in the migraine cycle at which the patient is recorded (17).

The paradigms known as paired associative stimulation (PAS) and short latency afferent inhibition (SAI), which combine peripheral and cortical stimulations with various interstimuli, are other techniques to research long-term learning mechanisms. The excitability of the sensory cortex typically reduces when a TMS pulse is delivered to the cortex before the peripheral sensory impulse enters the cortex; on the other hand, the excitability increases when the TMS pulse is delivered after the peripheral sensory impulse enters the cortex. Consistent with previous evidence (42,51), an inhibitory PAS paradoxically increases the amplitude of MEPs in patients with migraine without aura, whereas an excitatory PAS does not significantly increase the MEP. These paradoxical effects are dependent on the degree of excitability of the somatosensory thalamocortical circuit in a subset of patients (66). The homotopic muscle response elicited through motor TMS is inhibited by a peripheral afferent sensory volley employed in earlier experiments to explore both cortical GABAergic and thalamocortical cholinergic networks. In one study, patients with migraine without aura had lower levels of SAI during the preictal and ictal periods (67). Another study indicated that SAI was decreased in patients between attacks compared to healthy volunteers but increased during an attack. One study measured SAI based on each participant's SSEP N20 latency (68). By combining peripheral visual stimulation with TMS delivered over the visual cortex, PAS can also be examined over the visual system (69). According to this paradigm, a group of patients with migraine without aura cannot experience the typical opposing inhibitory/excitatory response that may be observed while assessing the habituation of VEPs in healthy participants (70).

Together, findings from magnetic and electrical neuromodulatory techniques applied to the sensorimotor and visual cortices demonstrate that migraine patients have altered physiological mechanisms of bidirectional synaptic plasticity potentiation/depression in the short

and long term, most likely because of altered thalamocortical control.

EEG studies in migraine

Clinical application of EEG analysis in migraine dates back to 1947 (71). Past studies have been largely inconsistent with regards to findings and methodologies (72). More recently, the mainstay of EEG research in migraine has relied on quantitative EEG (qEEG), which uses mathematical and statistical models, such as time and frequency analyses, analysis of connectivity and network approaches, to study neural dynamics. Most of the studies currently performed rely on the spectral decomposition approach, or spectral analysis, in which a temporal series of amplitude values are presented as a spectrogram of frequency bands, each representing an oscillating activity.

The study of coherence is also used in EEG investigations, being closely associated with spectral analysis. Coherence between signal is, in fact, the cross-power spectrum calculated as an index of the similarity, in terms of amplitude and frequency, of two signals, compared to level of similarity within the entire signals in each frequency band. EEG coherence provides an estimate of functional interactions between neural systems operating in each frequency band, yielding information about networks and integration across brain regions (73).

The principal finding obtained between attacks in migraineurs is represented by a diffuse slowing of background EEG activity, with reduction of the relative power in the high frequency bands (i.e. alpha and beta) and a simultaneous increase of low frequencies (i.e. theta and delta) (74).

This was partially confirmed in patients with migraine with aura, where a reduction of the beta band has been found with respect to other transient neurological conditions, while an increased alpha power was found in electrodes exploring the regions affected by the aura (75). A diffuse increase on theta band, more pronounced in migraine with aura, was also found in another study (76). In one study EEG was even able to discriminate between migraine with and without aura, finding higher theta band in patients without aura (77).

In migraine without aura augmented alpha power is found to be increased with respect to controls, although this funding is significant only in limited portions of the cerebral cortex, namely the right occipital area and precuneus (78). This is interesting because in a study on migraineurs an increased power of the lower alpha band (8–10 Hz) has been found after a visual task. Since the lower alpha band seems to be related to over-integration mechanisms, this could represent a marker of a tendency towards overstimulation in migraine (79). A recent study further confirmed a reduction of the spectral entropy of the low beta band encompassing fronto-parieto-occipital regions in episodic migraine compared with controls, as well as the presence of a high beta band which was able to differentiate CM from EM accurately (80).

However, some studies have found no significant changes in spectral EEG in interictal migraine, but rather determined profound changes in coherence between hemispheres in the beta and delta bands, suggesting reduced cooperation between hemispheres in migraineurs (81).

More recently, EEG analysis of microstates has allowed for a better understanding of interictal dynamics in migraine. Microstates are quasi-stable EEG configuration with durations spanning from milliseconds to seconds. The analysis of these rapidly fluctuating states can provide information at high temporal resolution regarding large-scale resting-state brain networks such as the visual, salience, and dorsal attentional network (82). Li et al. studied the percentage and the transitions among microstates in migraineurs, finding that migraine patients showed reduced activity of the salience network, and by contrast an increase in visual and dorsal attentional networks baseline activity (83).

With increased vicinity to an attack, the EEG signal in migraine shows a further tendency of widespread slowing, with increase in the relative power of lower frequency bands and a fragmentation of the symmetry of the alpha band in occipital regions, possibly indicating thalamocortical hypoexcitability (84). One study showed, up to 72 hours before the attack, an increase of the delta band localized in the same site later involved by the pain; 36 hours before the attack, delta power was more diffuse on the fronto-central brain regions (85). A recent study involving migraine patients carrying a mobile EEG device providedopposite results, however, highlighting a decrease of delta power and an increase of the beta band (86). Of note, this latter study is methodologically very different from the others.

Broader changes have also been reported, with one group finding that in the hours preceding an attack several EEG measures such as power, coherence and complexity tend to increase and 'normalize', becoming more similar to that of controls (87,88). The main limitation of these studies was that activity was recorded only from a small number of electrodes. In another study analyzing sleep, an increase of the average absolute value of the cortical activity was observed preictally in the brain region in which the pain would have later occurred, compared with nights of the interictal period (89).

By contrast, no significant EEG changes have been found in these same studies with regards to the postictal phase, both when using spectral analysis and complexity indexes (85–88).

EEG data regarding the ictal phase in migraine are not very consistent. Different studies have reported either increase (85) or decrease in the alpha band (90), while others could not find ictal alterations of the alpha, but rather determined an increase in the asymmetry between the two hemispheres (91,92). Most of these studies, however, are quite dated. A more recent study investigating brain activity in the ictal phase found an overall reduction of the alpha power and an increase of the theta, as well as an increase of the slow delta in the frontocentral regions, supporting EEG slowing during migraine attacks (93).

Cortical spreading depression detection

Finally, a field in which EEG is very promising lies in the understanding of the dynamics of cortical spreading depression. One international group, in particular, has studied the dynamics of CSD occurrence following brain trauma (94) and ischemia (95), and recently provided direct electrophysiological evidence for spreading depression as a pathophysiological correlate of aura (96). This was mostly possible thanks to routine preventive craniotomy of patients, which allowed guided EEG recordings via implementation of a cortical electrogrid.

Recordings of CSD in aura have otherwise been difficult, with some measures showing slower activity involving electrodes located over the hemisphere involved by CSD (75). Recently, however, a novel mathematical method was introduced to better detect regions of silence on EEG, which might prove useful to study CSD propagation in more detail (97). The major limitation of this new method is the reliance on baseline EEG to show significant differences, while the main advantage is that recording of a 160 second EEG epoch is determined sufficient to provide a result.

In conclusion, the majority of EEG studies performed on migraine patients have demonstrated a decrease in alpha rhythmic activity at rest and an excessive increase during a visual task; an increase in the power and coherence of theta (and sometimes delta) rhythmic activity at rest in all phases of the migraine cycle; and a decrease in beta-band oscillatory activity in patients with aura.

There is no simple explanation for these stable rhythmic brain changes during the phases of the migraine cycle. It is known that theta rhythmic activity facilitates the formation of associative memories, particularly episodic memory (98). In contrast, alpha-band rhythmic activity is more closely associated with the functional integrity of the thalamic pacemaker and thalamocortical loops (99). A steady pattern of reduced alpha and increased slow rhythms (theta-delta) with an alteration of accessory metrics, such as coherence and entropy, suggests a stable, probably genetically determined, thalamocortical dysrhythmia, which depends on aberrant brainstem to thalamus activation that in turn reduced cortical pre-activation (100,101). Nonetheless, this pattern of dysrhythmic activity could be responsible for functional alteration of cross-frequency coupling between different areas of the migraine brain involved in learning and plasticity processes (102,103). This coupling between cortical areas/networks is further compromised by aura occurrence, as highlighted by a decrease on neural beta oscillations, reflecting decreased global efficiency and less network integration in response to natural environmental stimuli (104), like light and sound.

Evoked potentials: A focus on SSEP and VEPs

Over the past few decades evoked potentials have been abundantly used to study the level of cortical excitability of the migraine brain. EPs have the advantages of offering excellent temporal resolution, of being relatively easy to perform and of allowing analysis of different sensory pathways within the central nervous system. Here we focus on the most studied sensory modalities in migraine: the visual pathway and the non-painful lemniscal sensory pathway, studied through the recording of visual VEPs and SSEPs, respectively.

Visual evoked potentials

Through appropriate tuning of the stimulation paradigm and the stimulus of VEPs, it is possible to study every pathway and station that forms the visual system. Initial studies in migraine examined the amplitudes of flash or patterned VEPs, with conflicting evidence (105–112). A few studies also focused on signalling from the innermost retinal layers (ganglion cells and fibres) through the recording of pattern electroretinogram, however no abnormalities were detected in both migraine with and without aura (113,114). By contrast, some of these initial studies did reveal an increased asymmetry between electrophysiological responses of the two hemispheres in migraine patients (110,112,113,115–120).

More recently, literature on neurophysiology of migraine has largely focused on the study of the habituation mechanism, defined as ‘a response decrement as a result of repeated stimulation’ (121). The biological behaviour of abnormal cortical information processing and lack of habituation fits well with the aversion that migraine patients feel towards any kind of sensory

stimulation, both in the ictal and interictal period (122). By using pattern-reversal VEP, most studies performed in interictal episodic patients have in fact shown deficient habituation to a stereotyped and repeated presentation of a visual stimulus, typically a checkerboard pattern (123–137).

Just as the pain of migraine can vary from day to day, so this electrophysiological behaviour can fluctuate in relation to the migraine cycle. Habituation deficit raises as the interval from last attack increases (129,138), while it normalizes during the attack (124,138,139) and after successful treatment (49,50,137,140,141). Subtle differences in VEP responses have also been found in subgroups of migraine with aura characterized by different clinical phenotypes (129,142).

Further evidence of this neurophysiological alteration is represented by the initial response amplitude of VEPs. Although most studies have failed to detect a clear statistical significance, this value tends to be reduced in migraine patients between attacks in comparison to healthy subjects, while it increases during attacks (50,101,123,134,139,143–145). This suggests that the abnormal cortical responsivity seen interictally in migraineurs may be due to a decreased cortical preactivation level or to subcortico-cortical metaplastic hyporesponsivity during initial stimulus repetition, rather than a simple general cortical hyperexcitability (146).

An explanation of this dis-excitability has been attributed to abnormal thalamic control over the flow of information reaching the cortex itself, leading to a functional disconnection of the thalamus and thus to decreased intracortical lateral inhibition (101). To investigate this, lateral inhibition was studied with VEPs by means of different visual stimulation paradigms, such as windmill/dartboard alternating patterns (138) and paired visual stimulations (147,148), confirming alterations of this cortical mechanism in migraine with and without aura.

Importantly, not all authors have detected a lack of interictal habituation studying VEPs (149–152). This is likely due to the large number of factors that can influence the behavioral phenomenon of habituation (153), such as: genetic factors (136), prophylactic treatments (140,141), sunlight irradiance (126), perceived stress (127), and visual stimulus properties, such as contrast or temporal and spatial frequencies (109,149,154,155).

Emphasizing how the electrophysiological properties of the brain can follow the phenotypic expression of migraine and its related syndromes, deficient VEP habituation was also described in patients affected by visual snow syndrome (VSS), which shares some pathophysiological mechanisms with migraine (156,157). Dysfunctional visual processing and cortical hyperexcitability have been hypothesized as possible pathophysiological mechanisms responsible for VSS (158). Case reports and case series have described the presence of a habituation deficit to VEPs in these patients, regardless of the presence (159) or absence of concomitant migraine (160,161). A broader cortical involvement beyond the primary visual cortex was detected in a single VSS patient by using a dual-stimulus stimulation paradigm, which showed multiple mechanisms of abnormal neuronal responsiveness localized mainly in extrastriate visual regions and at the cerebellar level (162). Interestingly, in these same regions previous neuroimaging studies had detected both increased metabolism (163) and grey matter volume (164). A different group, however, did not confirm a habituation deficit in VSS, and rather found that these patients are characterized by a delayed N145 latency and reduced N75–P100 amplitudes with VEPs, supporting the idea that visual snow syndrome is associated with disfunction of extrastriate cortical areas (165). Overall, small sample sizes may have influenced these differences in neurophysiological findings, and more studies with standardized protocols of examination are needed in order to better elucidate the pathophysiology of VSS, particularly with regards to the mechanisms it shares with migraine and aura.

Somatosensory evoked potentials

Similarly to what has been found with VEPs, several SSEPs studies have shown that episodic migraine patients in the pain free phase are characterized by an altered processing of sensory information, and in particular by a lack of habituation (166–169). In addition, patterns of habituation showed a direct link to the clinical fluctuations of migraine, with the magnitude of habituation deficit correlated with disease worsening (169). Similarly to the visual responses, it was suggested that habituation deficit could be explained by the lower cortical activation level depending on abnormal thalamic control (146). The reduced degree in lateral inhibition within somatosensory cortex is hypothesized to play a role in this habituation deficit (68).

Regarding baseline amplitude and latency of cortical SSEP responses, most studies did not find differences between interictal episodic migraineurs and healthy volunteers (166,167,170–172). However, one study found a significant asymmetry between the two hemispheres when recording the N30 SSEP amplitudes (172). Partially in line with the findings in VEP studies, an initial amplitude response potentiation was observed during the headache phase, which has been interpreted as a neurophysiological manifestation of central sensitization (168). More recently, the degree of somatosensory excitation (magnitude of initial response) and inhibition (paired-pulse paradigm) in both the brainstem and the somatosensory cortex was studied in two migraine women for 30 consecutive days

(173). The authors found that the degree of brainstem and parietal excitation was maximal, while the degree of inhibition was minimal, 24 hours before the onset of the headache. Of note, a recent study investigating the effects of concomitant visual and somatosensory stimulation in migraineurs between attacks suggests that the abnormal processing in sensory information is not limited to single modalities, but actually involves multisensory integration (174).

In summary, visual and somatosensory electrophysiological responses detected the existence of a state of latent hyper-responsiveness/lack of habituation to multimodal sensory stimuli during the pain-free period, which change shortly and revert to a state of transient central sensitization during a migraine attack. The interictal latent abnormalities may be considered a fertile dysexcitatory ground for the development of a new attack.

A proposed unified theory of electrophysiological changes underlying migraine recurrence

Since Liveing's theoretical definition of a migraine attack as a 'nerve storm' in 1873 (175), and almost eight decades since the first in-vivo electrophysiological changes observed in migraine patients (71), causative factors of migraine remain largely unknown. If they exist, these specific factors should be detectable outside of an attack, constituting genetically determined predisposing factors for recurrence. However, the 'holy grail' of genetics has yet to be discovered, most likely because there is no single migraine gene. Rather, it is believed that multiple genes can predispose individuals to both clinical manifestations of the disease, such as nausea/vomiting, photo and phonophobia. In many instances, the presence of numerous and diverse comorbidities is believed to further lower the threshold for migraine recurrence (176).

Electrophysiological techniques have revealed the following characteristics of the migraine brain: 1) a general unbalance between cortical inhibitory and excitatory behavioural neural activity; 2) a general inability to externally modulate the cortical neural circuits of the migraine patient in a physiological manner, both in the short and long term; 3) an alteration of cerebral rhythms both at rest and during a task, with a stable prevalence of slower (theta and delta) instead of faster (alpha and beta) rhythms; 4) a malfunction of thalamocortical rhythm control circuits. Knowing that the synaptic circuitry of the thalamus regulates cortical neuronal oscillations (177), a thalamocortical dysrhythmia, due to anatomo-functional thalamic disconnection from the brainstem (100), may be at the base of all the characteristics of the migraine brain mentioned above. However, most of these alterations are non-stationary, meaning that they vary plastically during the phases of the migraine cycle and the interictal phase.

In conclusion, electrophysiology has demonstrated that the migraine brain is distinguished by continuous and recurrent plastic changes in the functional activity of the brainstem-thalamus-cortex loop. Considering the central role of these structures in the selection, elaboration, and learning of sensory information, these functional alterations could be a sign of underlying chronic, probably genetically determined, dysfunctions of the synaptic short- and long-term learning mechanisms, which physiologically underlie habituation and sensitization phenomena (Figure 2) (178).

Synaptic plasticity refers to the ability of synapses to adjust their relative strength based on the overall level of activity or specific activity patterns, typically through dynamic regulation of receptor-synaptic scaffold interactions or trafficking. It plays a significant role in dendritic growth, synaptogenesis, and the formation of neural circuits during development. Synaptic plasticity is responsible for synapse remodelling during experience in mature neurons. From research on neurodevelopmental and neurological disorders, such as epilepsy and autism (179), it is well known that genetic mutations or pathology can lead to altered excitatory or inhibitory neurotransmission or impaired synaptogenesis, which typically results in synaptic plasticity deficits (180).

Homeostatic and Hebbian plasticity are two major types of activity-dependent synaptic transmission regulation (181). Throughout Hebbian plasticity, synapses respond dynamically in the same direction as the applied stimulus. These Hebbian mechanisms result in a persistent strengthening or weakening of synapses, termed glutamatergic AMPA receptors and NMDA receptor-dependent LTP and GABA type-A receptor-dependent LTD, respectively. During homeostatic plasticity, however, synapses respond in the opposite direction and on a slower timescale than the applied stimulus, compensating for the shift in activity in order to preserve information processing and network stability (182).

These dysfunctions of synaptic plasticity may alter the normal balance between feedback and feedforward mechanisms of interactions between subcortical and cortical structures that are responsible for adaptation and protection against an excessive load of sensory stimuli. There is a need for additional research that simultaneously investigates excitatory and inhibitory synaptic responses under various plasticity-inducing protocols, with a particular focus on the thalamic level and mechanisms of thalamic-cortical crosstalk. In addition, research should investigate whether the malfunctioning of these fundamental learning mechanisms in migraine, by reorganizing neural maps in the downstream cortical networks, could lead to maladaptive changes in the interpretation of incoming sensory

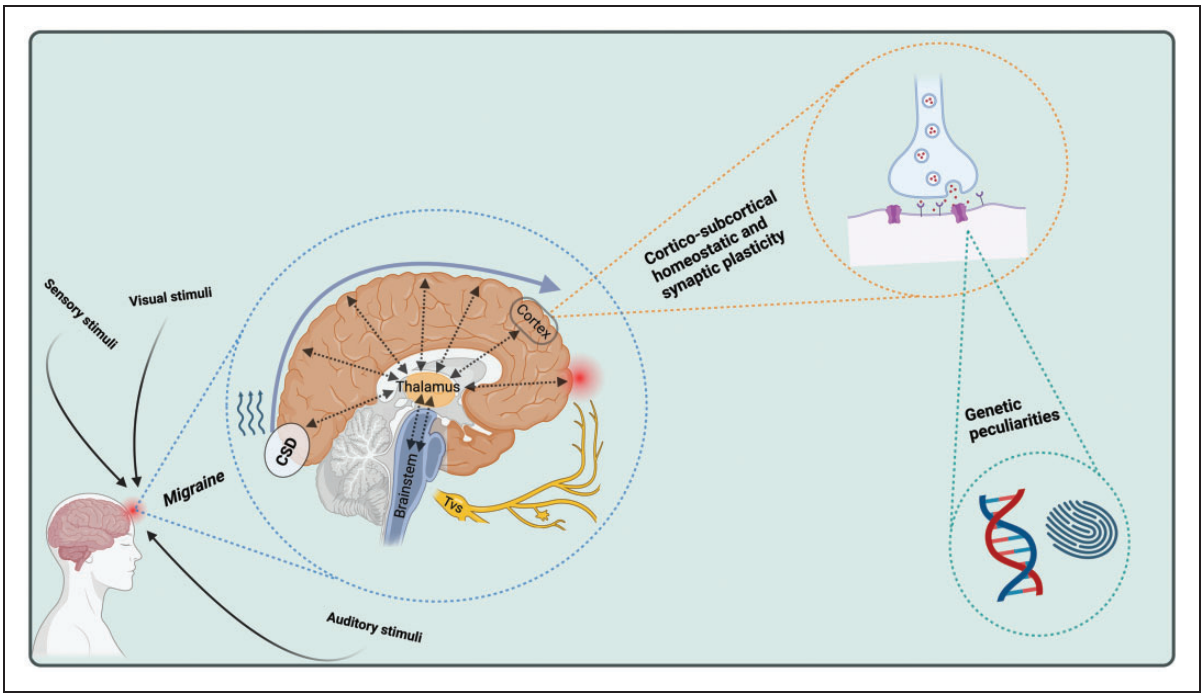

Figure 2. Proposed theory of electrophysiological changes underlying migraine recurrence. Created with BioRender.com.

information, such as photo- and phonophobia, allodynia, and visual snow. However, additional research is required to determine whether these same mechanisms can account for the structural and functional abnormalities repeatedly detected by modern neuroimaging techniques in both young and adult migraineurs (183).

Uncovering the mechanisms governing synaptic plasticity will shed light on how disruptions in the physiological balance between GABAergic and glutamatergic function influence the pathophysiology of migraine disorder, identify new therapeutic targets, and reveal the potential consequences of pharmacologically targeting these receptors.

Article highlights

- This review highlights the main electrophysiological changes in brain dynamics across the different phases of the migraine cycle, by summarizing studies using transcranial magnetic stimulation, electroencephalography and non-painful evoked potentials.
- Electrophysiology in migraine shows dynamic and recurrent functional alterations within the brainstem-thalamus-cortex loop, which suggest chronic, probably genetically determined dysfunctions of the synaptic short- and long-term learning mechanisms.

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