

The Role of Electroencephalography in the Evaluation of Patients With Migraine and Tension-Type Headache

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SUMMARY

Headache disorders are one of the most prevalent and disabling conditions worldwide. Headache is classified as primary or secondary according to its underlying pathophysiology. The most common primary headaches are migraines and tension-type headaches (TTH). Their diagnosis is based mostly on clinical presentation, but sometimes this can be challenging. In order to improve the differential diagnostics of these conditions, we evaluated the role of electroencephalography (EEG) in diagnostic workup.

EEG records electrical activity of the brain cortex. It is mostly used to diagnose epilepsy, but EEG abnormalities are found in many headache patients as well. In this review, we provide an overview of EEG-based headache-related research. We compare their results in the hope of better understanding the neural changes in migraine and TTH. According to our findings, EEG might be helpful in the search for potential headache biomarkers, but further studies are necessary.

KEYWORDS

EEG; Migraine; Tension-type headache; Neurophysiology

Introduction

Headache is the symptom of pain in the face, head or neck, and is usually classified as primary or secondary. Primary headaches are recurrent headaches not caused by an underlying disease or structural

problems. Secondary headaches are caused by an underlying disease (infection, head injury, vascular disorders, brain bleed, tumors, etc.). A primary headache is diagnosed through medical history and a physical examination. The most common types of primary headaches are migraines and tension-type

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headaches (TTH), with the latter also being the most common type of headache in the general population.

The European Federation of Neurological Societies (EFNS) guidelines for the diagnosis of primary headaches report that an interictal electroencephalography (EEG) is not routinely indicated for headache diagnosis. The usual indication of an EEG in headache patients is for a differential diagnosis when there is a serious doubt of epileptic seizure as the underlying condition, especially in headache patients with atypical auras or episodic loss of consciousness. If a patient has a headache with a visual aura or brainstem aura, an EEG can be performed to differentiate its symptoms from those of epilepsy (Figure 1)¹.

TTH is characterized by non-throbbing pain, which is usually bilateral. It is usually mild to moderate in intensity and is the most common type of headache. It can occur with or without pericranial muscle tenderness. According to frequency, TTH can be episodic (1–14 days with headache a month) or chronic (more than 15 days with headache a month). Due to its high prevalence, TTH is

an important cause of disability of the working age population.

Migraine is characterized by throbbing or pulsatile pain, which is usually severe. The pain is mostly unilateral and aggravated by physical activity. Approximately one billion people globally are affected by migraine.

Migraine may be preceded by aura. Aura is mostly visual, but it can also include other symptoms, such as sensory, motor or language disorders¹.

The pathophysiology of migraine is complex and still not completely understood. The most accepted theory is that migraine is caused by cortical spreading depression: a cortical electrical activity event, which causes aura, activates the trigemino-vascular system and alters the blood-brain barrier permeability².

Although increasing numbers of studies have been searching for a specific migraine biomarker and its pathogenesis, they remain to be found.

EEG is a non-invasive, low-cost diagnostic method that records the electrical activity of the brain cortex. It is an important diagnostic test in

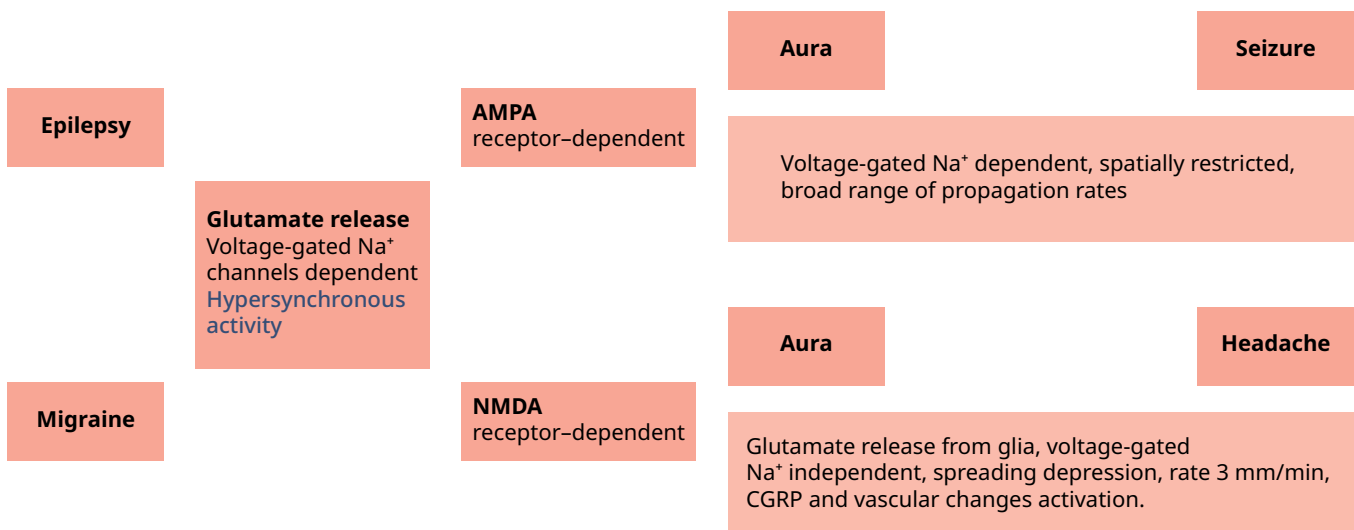


FIGURE 1. Changes of electrical brain activity in epilepsy vs migraine patient.

the evaluation of potential epilepsy, but many EEG changes can be caused by different conditions, including headaches. These changes present as a shift from the alpha rhythm (8–12 Hz) — the rhythm adults usually have when they are awake with their eyes closed — and can be described as epileptiform activity or nonepileptiform abnormalities. Nonepileptiform abnormalities include changes in wave amplitude, as well as slowing and asymmetry.

The purpose of this review was to provide an overview of the findings of electrophysiology studies aiming to investigate EEG changes in patients with migraine or TTH.

EEG studies

A commonly used method to interpret EEG signals is spectral power analysis. It recognizes four frequency bands: delta (0–4 Hz), theta (5–7 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–100 Hz). When awake with their eyes closed, adult humans are normally in the alpha rhythm.

With EEG power spectral analysis, we can interpret peak and median frequency, and total, absolute and relative power, as well as to determine the presence of any asymmetry³.

One study found that 36% of migraine patients and 12% of patients with TTH who were included in the study had specific EEG abnormalities during headache attacks. When compared with a headache-free period, only 16% of migraine patients and 2% of TTH patients had specific EEG abnormalities⁴.

Different EEG changes are usually found when comparing healthy controls and migraine patients. A comprehensive study found significant changes when comparing migraine patients with and without aura, but also in migraine patients with episodic and chronic headache³.

In their study, Bjork et al.⁵ analyzed EEG changes in migraine patients and healthy controls. By

analyzing the asymmetry of frequency bands, and absolute and relative power, they found globally increased theta activity in migraine patients compared with healthy controls. Their results also showed that decreased peak frequency could correlate with an increased duration of disease.

Clemens et al.⁶ analyzed alpha frequency in untreated migraine patients without aura. Their results showed significant spectral differences only in the right occipital region.

Visual perception is considered to be regulated by fluctuations in alpha oscillation. O'Hare et al.⁷ found that increases in alpha power are lower in migraine patients compared to healthy controls.

Another study that included migraine patients and healthy controls compared alpha power before and after a visual stimulus. Their results showed that alpha power in migraine patients was significantly reduced before stimulus onset, which may indicate that migraine patients have a hypersensitive visual cortex⁸.

Changes in frequency bands were also observed depending on migraine cycle. In a study done by Martins et al.⁹, the authors found a significant decrease in delta bands and increase in beta bands that occur 24 hours before a headache. Their results confirmed that EEG could detect changes before migraine attacks.

In another study, researchers found that patients who have migraine with aura showed alpha rhythm and peak frequency asymmetries over posterior regions¹⁰ and a widespread increase in delta¹¹ and theta power during the interictal period¹⁰. If aura is prolonged, the reduction of alpha activity may be associated with slow waves increase¹². Migraine patients with pure visual aura mostly have a reduction of alpha rhythm¹³, or a unilateral decrease in alpha and theta activity¹⁴.

Some studies have shown a mild asymmetry of slow waves contralateral to the visual field defect during visual aura^{15,16}, while some patients have shown the same slow waves in the interictal period¹⁵.

Bjork et al.¹⁷ found that higher theta power and photoresponse inhibition were associated with higher trigger sensitivity and symptom severity.

Mykland et al.¹⁸ compared cyclic changes from the interictal baseline to the preictal, ictal and post-ictal phases. They also compared interictal beta event-related desynchronization (ERD) between migraine patients and healthy controls. ERD is an electrophysiological feature that represents an induced, time-limited, non-phase-defined response to events, and is specific to EEG frequencies¹⁹. The results of the study by Mykland et al. showed significantly increased beta power in the preictal phase compared to the interictal phase. By analyzing changes in the interictal period, they found that contralateral beta-ERD was stronger at the contralateral side in migraine patients, but also in healthy controls. They also concluded that higher preictal baseline beta activity in migraine could perhaps present as decreased activation in the sensorimotor cortex in the ictal phase¹⁸.

Gomez-Pilar et al. proposed that future studies based on EEG pay attention to medium and fast frequency, especially the beta band²⁰. Contrary to this, Zhang³ proposed that future migraine studies based on EEG pay attention to brain activity in lower frequency bands. The differences in the outcomes of those studies point to a lack of consensus on the focus of EEG diagnostics.

Studies that investigated EEG in TTH are scarce. Their results are inconsistent and disappointing,

so the general conclusion is that EEG in TTH is not very useful as a diagnostic tool. In one study, they found that EEG is not helpful in distinguishing TTH from migraine²⁰ and in another that EEG is not helpful in distinguishing primary from secondary headaches²¹. It has been discovered that in patients who suffer from chronic TTH, central sensitization probably plays a decisive role^{22,23}. In a study by Buchgreitz et al., they investigated the spatiotemporal aspect of brain activity during and after induced muscle pain in patients with chronic TTH and healthy controls, but their results suggest that there is no difference in cortical projection between the two groups²⁴.

Microstate analysis

EEG microstates are patterns of potential topography recorded by scalp EEG that change dynamically and in an organized manner over time^{25,26}.

The analysis of EEG microstate characteristics offers the possibility to explore the neurobiological mechanisms underlying altered cortical excitability and aberrant sensory, affective and cognitive processing, thus deepening our understanding of migraine pathophysiology. It is well known that during migraine attacks a wave of “spreading cortical depression” occurs with underlying chemical

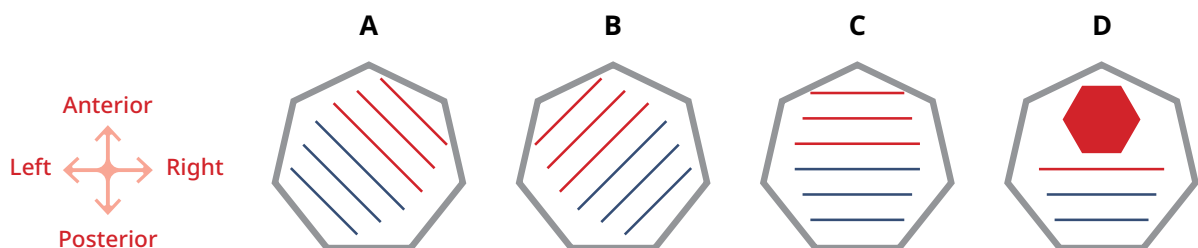


FIGURE 2. Schematic view of the microstates concept

A: right-frontal to left-posterior, B: left-frontal to right-posterior, C: frontal to occipital, D: mostly frontal and medial to slightly less occipital activity than class C.

and electrical changes in brain activity, usually spreading from the occipital lobe. The spatial configurations can be divided into four categories labeled A–D (Figure 2)^{25–27}. They remain stable for a certain time (60–120 ms) and then change to another configuration, which again remains stable for a certain time²⁷.

EEG microstates are widely used in psychiatric and neurological disorders. In the past few years, EEG microstates have also been used to assess resting brain changes in migraine patients with or without aura^{28,29}. The characteristics of EEG microstates can be helpful in the investigation of migraine pathophysiology.

Li et al.²⁸ compared resting EEG in migraine patients and healthy control subjects. They compared microstate parameters among them and found that microstates B and D showed a higher incidence in migraine patients compared to healthy controls, while microstate C negatively correlated with the clinical measures of headache-related disability. They also found that microstate B was associated with changes in the visual network involving bilateral visual areas.

In their study, Zhou et al.²⁹ found that microstate B was increased and microstate D decreased in migraine patients without aura.

Lei et al.²⁵ compared microstate parameters in migraine patients with or without aura and healthy controls. Their results showed that microstate B correlates with headache frequency in migraine patients without aura. The same group of patients also had a significantly enhanced transition from microstate B to microstate D. Their results also showed that microstate B parameters were reduced in migraine patients with aura compared to patients without aura²⁶.

Although research on microstate parameters in migraine patients remains limited, we can conclude that the probability of transition between microstate B and microstate D is increased in migraine patients without aura compared to healthy controls, despite conflicting findings from Zhu et al²⁹.

Still, the presence of an abnormal microstate D in migraine patients without aura can be considered established.

Machine learning and deep learning

Recent studies increasingly use machine learning to analyze data in their research. A great advantage of using machine learning in EEG analysis is that it gives us a greater ability to not only identify the response to a given stimulus, but also to predict the perception and response to the same stimulus or experiment^{30,31}. A further advantage of machine learning is its ability to extract all relevant parameters, allowing researchers to prioritize features within their specific area of interest. Machine learning algorithms can be applied to quantitative EEG data for outcome prediction, artifact removal, prospective selection or pattern recognition.

Deep learning is a type of machine learning based on neural networks that can be very effective in identifying pain-related features in EEG³². Compared to machine learning, deep learning might have an additional advantage; as it has the ability to learn features automatically, there is no need to pre-extract features.

Lately, several studies have used EEG and machine learning in diagnosing migraine and for predicting therapeutic responses in migraine patients. In a study done by Kim et al.³³, they investigated the potential of qEEG as a biomarker for diagnosing and monitoring therapeutic effects in migraine patients. Their results showed that, compared to the healthy control group, the cohort had a tendency to increase absolute power in all frequencies, especially in beta bands³³. In another study comparing migraine patients and healthy controls, the authors investigated specific frequency bands that might have the ability to discriminate chronic and episodic migraine.

They found two specific frequency bands: one for comparing migraine patients and healthy controls (11.6–12.8 Hz), and the other for comparing episodic and chronic migraine (24.1–29.8 Hz)³⁴. Subasi et al. used deep learning in their study using the discrete wavelet transform and Random Forest algorithm, and successfully distinguished migraine patients from the healthy controls³⁵. In another study by Yin et al., the authors found a clear distinction between TTH and migraine³⁶.

Orhanbulucu et al. performed a study involving 18 migraine patients and 21 healthy controls. They analyzed EEG signals based on resting state, and visual and auditory stimuli, and concluded that it might be possible to classify migraine patients using signal processing and deep learning methods³⁷.

According to all of the results listed so far, machine-learning studies have the potential to help us diagnose primary headaches, especially when we are in doubt as to the type of primary headache³⁸. Nevertheless, as studies using EEG signals with machine learning and deep learning models are rare, and these methods are still not widely available, further studies are needed to establish proper and replicable methodologies.

Discussion

The advantage of using EEG in painful conditions is its high temporal resolution, which is crucial for understanding pain, as it is a dynamic process^{39,40}. Additionally, EEG is low-cost, widely available and easy to use. These practical strengths have facilitated extensive research in TTH and migraine, revealing a complex picture of both hyper- and hypoexcitability. Bjork et al.¹⁷ found global slowing and reduced photic responses supporting hypoexcitability. Conversely, many other studies have linked TTH and migraine to hyperexcitability, reporting

decreased power in delta and theta frequencies, and increased beta power^{41,42}.

Another interesting research point is the fact that migraine and epilepsy are prototypical examples of paroxysmal brain disorders. While migraine-like headaches are quite frequently seen in the epileptic postictal period, sometimes epileptic seizures occur during or following a migraine attack. This rare phenomenon is sometimes referred to as migralepsy and was originally described in patients with migraine with aura. Current evidence does not support an association with migraine without aura.

While recent studies increasingly utilize functional MRI, PET, MEG and evoked potentials, these methods are still not widely available, which limits their applicability^{34,42,43,44}. Most of the studies using these methods found changes in pain-related brain circuits (thalamus, amygdala, etc.) and in beta bands in the EEG. According to their results, future studies should pay attention to specific brain regions and try to correlate EEG frequencies with functional MR, PET, MEG, and evoked potentials in order to establish diagnostic and prognostic values in migraine and TTH²⁰.

Based on the aforementioned information, we can conclude that future studies should focus on fast frequencies regardless of the type of analysis they use.

Machine learning has great potential to help us identify an objective biomarker that could facilitate not only finding the best optimized treatment for each patient with primary headache, but also predicting patients' responses to treatment³⁸.

Deep learning is a machine learning method where features are learned automatically, making it superior to machine learning methods. Both methods, especially deep learning, have great potential in diagnosing neurological diseases³.

Although preliminary findings suggest potential biomarkers, rigorous testing is still necessary to confirm their reliability and safety. ■

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SAŽETAK

Uloga elektroencefalografije u dijagnostici migrenske i tenzijske glavobolje

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Glavobolja je jedan od najčešćih poremećaja koji uzrokuju onesposobljenost u cijelom svijetu. Glavobolja se klasificira kao primarna ili sekundarna prema temeljnoj patofiziologiji. Najčešće primarne glavobolje su migrena i glavobolja tenzijskog tipa. Njihova se dijagnoza uglavnom temelji na kliničkoj slici, ali ponekad može biti izazovna. U svrhu poboljšanja diferencijalne dijagnostike ovih stanja istražili smo ulogu elektroencefalografije (EEG) u dijagnostičkoj obradi ranije navedenih stanja u znanstvenoj literaturi.

EEG bilježi električnu aktivnost moždane kore. Uglavnom se koristi za dijagnosticiranje epilepsije, ali EEG abnormalnosti nalaze se i kod mnogih pacijenata s glavoboljom. U ovom literaturnom pregledu dajemo presjek EEG istraživanja povezanih s glavoboljom. Uspoređujemo njihove rezultate u nadi da ćemo bolje razumjeti neuralne promjene kod migrene i glavobolje tenzijskog tipa. Prema rezultatima, EEG bi mogao biti od pomoći u potrazi za potencijalnim biomarkerom glavobolje, ali su potrebne daljnje studije.

KLJUČNE RIJEČI

EEG; Migrena; Glavobolja tenzijskog tipa; Patofiziologija