Pain Medicine, 0(0), 2020, 1–9
doi: 10.1093/pm/pnaa117
Original Research Article

Exploring EEG Spectral Patterns in Episodic and Chronic Migraine During the Interictal State: Determining Frequencies of Interest in the Resting State

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Funding sources: This research was supported by the European Commission and the European Regional Development Fund (FEDER) under the project "Análisis y correlación entre la epigenética y la actividad cerebral para evaluar el riesgo de migraña crónica y episódica en mujeres" (Cooperation Programme Interreg V-A Spain-Portugal, POCTEP 2014–2020), by the Ministerio de Ciencia, Innovación y Universidades, and FEDER under project DPI2017-84280-R, by "Gerencia Regional de Salud, Consejería de Sanidad, Junta de Castilla y León" under project "Parámetros espectrales y no lineales en electroencefalograma basal en pacientes migrañosos" (GRS 1257/A/16), and by CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN) through the Instituto de Salud Carlos III co-funded with FEDER funds.

Conflicts of interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abstract

Objective. The analysis of particular (electroencephalographic) EEG frequency bands has revealed new insights relative to the neural dynamics that, when studying the EEG spectrum as a whole, would have remained hidden. This study is aimed at characterizing spectral resting state EEG patterns for assessing possible differences of episodic and chronic migraine during the interictal period. For that purpose, a novel methodology for analyzing specific frequencies of interest was performed. **Methods**. Eighty-seven patients with migraine (45 with episodic and 42 with chronic migraine) and 39 age- and sex-matched controls performed a resting-state EEG recording. Spectral measures were computed using conventional frequency bands. Additionally, particular frequency bands were determined to distinguish between controls and migraine patients, as well as between migraine subgroups. **Results**. Frequencies ranging from 11.6 Hz to 12.8 Hz characterized migraine as a whole, with differences evident in the central and left parietal regions (controlling for false discovery rate). An additional band between 24.1 Hz and 29.8 Hz was used to discriminate between migraine subgroups. Interestingly, the power in this band was positively correlated with time from onset in episodic migraine, but no correlation was found for chronic migraine. **Conclusions**. Specific frequency bands were proposed to identify the spectral characteristics of the electrical brain activity in migraine during the interictal stage. Our findings support the importance of discriminating between migraine subgroups to avoid hiding relevant features in migraine.

Key Words: Chronic Migraine; Episodic Migraine; Migraine Duration; Hyperexcitability; Neural Oscillations

Introduction

Migraine is a complex pathophysiology in which the underlying mechanisms could be hidden by a number of confounding factors, such as interindividual diagnostic differences (number of days of migraine, presence of aura, and ictal or interictal situation, among others). This could be a reason for the contradictory results usually reported in migraine studies, both those based on electroencephalographic (EEG) signals [1–3] and on functional resonance imaging (fMRI) [4,5]. Nonetheless, it is commonly accepted that migraineurs share common characteristics, such as the influence of genetics [6] or hormonal

factors [7]. Evidence of altered brain excitability has been previously reported both in EEG [2] and magnetoencephalographic studies [8].

Migraine can be subtyped as episodic migraine (EM) and chronic migraine (CM). This split is based on the frequency of headache days, with EM being migraine with headache frequency <15 days per month and CM being migraine with headache occurring on ≥15 days per month during at least three months, fulfilling at least eight of the criteria of migraine pain [9]. It is reasonable to hypothesize that spectral features of brain dynamics are different in EM compared with CM. Besides, medication overuse, one of the risk factors for migraine chronification, has long been known to produce changes in the brain waves [10], an increase of the EEG power spectrum in specific frequency bands [11], or a decrease in linear connectivity [12], depending upon the particular drug. These changes in the spatiotemporal structure of the ongoing brain activity take time. Therefore, both illness duration and illness subgroups are relevant features involved in migraine characterization.

The cortical disturbances that affect migraine patients (MPs) may be recorded with adequate spatial and temporal resolution. Thus, EEG is presented as an appropriate technique for monitoring brain activity. Additionally, it is the most used technique in the clinic due to the additional advantages of EEG, such as portability, relatively simple and inexpensive equipment, and noninvasiveness. Hence, findings obtained using EEG can be easily exported for daily use in the clinic. Despite some previous EEG studies supporting the existence of cortical dysfunction in migraine, discordant results showing both cortical hypo- and hyperexcitability have been suggested [13,14]. On the one hand, these controversies could be due to discrepancies in the moment of recording with respect to the migraine cycle [2]. Timing of the recording in relation to the migraine attack becomes a major issue, making it necessary to study each cycle separately. To the best of our knowledge, only one excellent study has previously addressed an EEG-based spectral analysis characterizing the migraine stages [2]. This study, however, did not distinguish between EM and CM subgroups. On the other hand, another cause of controversy could be the well-known interindividual differences in the conventional definition of the frequency bands. Frequency bands and their relationship with cognition can vary slightly from subject to subject, making the comparison between spectral patterns biased [15]. To address this issue, studies should focus not only on conventional frequency bands, but also on the specific sub-bands that provide information relevant to the discrimination of migraine as a whole or its subgroups (EM and CM) during a particular stage of the migraine cycle.

This body of evidence and considerations led us to hypothesize that the split into migraine subgroups (EM and CM), as well as the analysis of specific frequency sub-bands, is relevant to the determination of migraine underpinnings, particularly spectral patterns and their relationship with illness duration. In concordance with this hypothesis, this study is aimed at characterizing spectral resting state EEG patterns of EM and CM during the interictal period. For that purpose, features of spectral power, spectral slowness, primary neural oscillation, and spectral regularity were calculated. These features were obtained using relative power (RP), median frequency (MF), individual alpha frequency (IAF), and spectral entropy (SE), respectively. To address the issue of interindividual frequency differences, an analysis of the frequencies of interest (FOI) was performed in order to search for trends in the spectrum that distinguish between groups.

Methods

Participants

Outpatients in their first visit to the Headache Unit were recruited from the Clinical University Hospital of Valladolid (Spain), a tertiary center. Diagnosis was conducted according to the criteria of the International Classification of Headache Disorders, third edition, beta version (ICHD-III beta, 2013) [10]. Patients were asked to keep a headache diary to determine migraine phases. They were split by two expert neurologists according to the International Classification of Headache Disorders [10] based on the frequency of headache days: i) episodic migraine (headache occurring on <15 days per month on average) and ii) chronic migraine (with ≥15 headaches per month, eight of these with migraine-related characteristics). As it is still an open debate as to whether high-frequency episodic migraine (nine to 14 days of headache per month) has different psychological underpinnings than chronic migraine, we have not included such patients in our study. We collected sociodemographic and clinical data from all patients, including the duration of migraine disease (years), headache frequency (days per month), and time from onset of chronic migraine (months) when applicable. Patients with other neurological or psychiatric illness, preventative intake, drug abuse, or history of traumas that could affect the EEG were excluded from the study. Patients in the ictal or postictal period were also excluded. Finally, a total of 87 patients with migraine (45 episodic and 42 chronic patients) were included in the study. A careful clinical examination of each participant was conducted to determine inclusion and exclusion criteria. For healthy controls, this meant that the participant was excluded if they showed a present or past medical history of migraine.

Age- and sex-matched healthy controls were recruited from hospital colleagues and their relatives or friends. In this study, 39 healthy controls were included to compare with migraine EEG patterns.

Sociodemographic and clinical data are included in Table 1. All participants read and signed a consent form before their participation. The local Ethics Committee of

Table 1. Sociodemographic and clinical data from healthy controls and migraine patients

						HC vs MP		EM vs CM	
		HC	MP	EM	CM	U/χ^2	P	U/χ^2	P
Sociodemographic data	N	39	87	45	42	–	–	–	–
	Age, y	33 (17)	39 (19)	35 (19)	42 (18.75)	$U = 2{,}121$	>0.05	$U = 1{,}686$	**0.012**
	Sex (male:female)	29:10	68:19	34:11	34:8	$\chi^2 = 220$	>0.05	$\chi^2 = 0.371$	>0.05
Clinical data	Presence of aura (yes:no)	–	6:79	3:42	3:39	–	–	$\chi^2 = 0.008$	>0.05
	Duration from migraine onset, y	–	15.8 (12.1)	6.8 (7.7)	25.5 (7.7)	–	–	$U = 2{,}682$	**1E-12**
	Duration in the CM state, mo	–	–	–	34.9 (36.8)	–	–	–	–

As data do not meet parametric assumptions, median and interquartile range were reported as mean (interquartile range). Statistical differences between groups were reported using the Mann-Whitney U test or chi-square test, as appropriate.

Statistically significant differences are marker in the table in bold.

CM = chronic migraine; EM = episodic migraine; HC = healthy controls; MP = migraine patients.

University Hospital of Valladolid approved the study (PI: 17.528).

EEG Acquisition

EEG recordings from patients in the interictal state (i.e., no migraine pain reported in the last 24 hours) were performed during the afternoon. Patients with migraine pain in the last 24 hours (i.e., during the ictal or postictal state) were not included in this study. As for patients, EEG signals from HCs were recorded during the afternoon to avoid circadian rhythm effects in the EEG [16]. All the recordings were made in the same room with the participants sitting and relaxing with their eyes closed.

EEG signals were acquired using a 32-channel system (BrainVision, Brain Products GmbH), with active electrodes inserted in an elastic cap according to the international 10–10 system. The impedance was kept <5 kΩ during the recordings, and the Cz electrode was used as the reference electrode. Specifically, 10-minute EEG recordings were acquired while subjects were comfortably seated with their eyes closed. Drowsiness episodes, muscle activity, eye-related noise, and other artifacts were controlled and documented by an expert during the EEG acquisition.

Data were collected with a sampling rate (s_r) of 500 Hz. For online visualization purposes, hardware EEG filters were set at 0.016 Hz high-pass with a notch filter at 50 Hz. However, raw EEG data were used for subsequent offline analyses.

EEG Data Preprocessing

All the analyses, including preprocessing steps as well as spectral and statistical analysis, were performed using customized scripts of Matlab (R2017a) software (Matlab scripts regarding preprocessing are available upon request to the corresponding author) and the Statistics and Machine Learning Toolbox.

First, signals were re-referenced to the average activity of all active sensors. Second, data were filtered between 1.5 and 70 Hz by means of a band-pass finite impulse response filter. A zero-phase 50-Hz notch filter was applied to remove the power line artifact. Third, the continuous EEG was segmented into epochs of five-second length. Each epoch was individually inspected by an expert, removing those with any artifact. Finally, five minutes (60 epochs) free of artifacts per channel and subject were selected from a total of 10 minutes. The selection of these epochs was done blinded to diagnostic group. Five subjects were removed from the study due to excessive artifacts. The previously reported number of subjects (45 with episodic migraine, 42 with chronic migraine, and 39 healthy controls) was the same after this selection.

Spectral Analysis

To characterize the spectral content of EEG data, Fourier transform was used in an epoch-based way. Hence, the power spectral density (PSD) for each EEG epoch was computed. The discrete PSD was computed as the Fourier transform of the autocorrelation function. Thus, with each epoch of $N = 2,500$ samples, the autocorrelation function was a vector of $2N - 1 = 4,999$ samples with a frequency of $\left[\frac{-S_r}{2}, \frac{S_r}{2}\right]$ Hz, reaching a spectral resolution of 0.1 Hz. In the present study, PSD was normalized dividing by its own total area, so that the resulting normalized PSD (PSD_n) can be interpreted as a probability density function. This normalization is needed to compute the SE, whereas the other spectral parameters computed in this study are invariant with respect to such normalization.

Spectral content was characterized using four complementary measures [3]: i) relative power (RP), ii) median frequency (MF), iii) individual alpha frequency (IAF), and iv) spectral entropy (SE). These measures are meaningful under the hypothesis of stationarity that is not respected by EEG signals. However, epochs from resting-state EEG with up to a 10-second duration can be assumed to be wide-sense stationary [17].

RP is a conventional spectral measure that represents the area under the PSD_n in a specific frequency range. In this study, RP was computed in each of the conventional EEG frequency bands: delta (δ, 1.5–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–13 Hz), beta-1 (β1, 13–19), beta-2 (β2, 19–30 Hz), and gamma (γ, 30–70 Hz).

MF is defined as the frequency that comprises 50% of the power. It offers a way of summarizing the whole spectral content of the EEG.

IAF characterizes the spectral distribution of the alpha frequency band. Its importance lies in that alpha oscillations are dominant in the EEG of resting healthy subjects with their eyes closed [15], which is reflected in a peak in the PSD_n centered on the alpha band. IAF was therefore computed as the MF in the extended alpha band (7.5–12.5 Hz) [18].

SE is a measure of spectrum regularity. A signal with few spectral components reaches an SE value close to zero. On the contrary, a signal with several spectral components, which has the energy distributed over the whole spectrum (like white noise), yields an SE value close to 1.

Frequencies of Interest Analysis

The designation of the conventional frequency bands in the EEG has its origins in the particular distribution over the scalp of such frequencies. In addition, a close relationship between the amplitude and synchrony of the neural oscillations in specific EEG frequency bands and a variety of cognitive and perceptual functions has been demonstrated [19]. These bands, however, can be partitioned to look for characteristics only present in particular sub-bands [20–22]. This partition is subjective and has a strong dependence on interindividual variance. In order to take into account this variability, individual frequencies were defined on the basis of the IAF following the well-established procedure in Klimesch [15]. As the results reported in the Supplementary Data show (Supplementary Data), these frequency bands still did not allow us to distinguish between the migraine subgroups investigated in this study. To consider and detect common characteristic frequencies between groups, an FOI analysis was applied comparing all the individual frequencies between healthy controls and patients. The FOIs were determined as the frequencies of the PSD_n in which a trend in the spectrum could indicate between-group differences in spectral characteristics. Particularly, a band of interest for each comparison was defined as the continuous and maximum-length band in which statistically significant differences were found. For that purpose, a P value threshold of 0.05 was used after false discovery rate (FDR) correction. To remove spurious trends, the frequency bands <1 Hz were dismissed. Note that we were focused on detecting trends in the spectrum to identify specific frequencies to discriminate between groups. From the identified frequency bands of interest, later steps were aimed at computing spectral features for the characterization of each group.

Statistical Analysis

First, we checked for normality and homoscedasticity of the data by means of the Kolmogórov-Smirnov test and Levene test, respectively. As the data did not meet parametric assumptions, between-group statistical differences were assessed using the Mann-Whitney U test with a P value <0.05 as the threshold of significance. Spearman's correlation was used to assess the monotonic relationship between clinical and spectral parameters of the EEG. The chi-square test was applied to categorical data. Finally, an FDR-controlling procedure was used to control for multiple comparisons (one comparison per EEG electrode) [23].

Owing to the imbalance of the population mainly due to the HC group, a bootstrapping approach was followed to determine the FOI. For that purpose, 39 subjects (the same as the total number of healthy controls) were randomly selected from the patient group. Then, the Mann-Whitney U test was performed for each frequency for the HCs and the 39 selected patients. This procedure was repeated 1,000 times, obtaining 1,000 different statistics associated with each iteration. Therefore, the possible bias due to the influence of the unbalanced groups was minimized. The same procedure was used to compare spectral and nonlinear measures in the HC and MP groups.

Results

Spectral EEG Characteristics in the Conventional Frequency Bands

Each measure was averaged across artifact-free epochs and then assessed by means of i) a grand-average approach and ii) a sensor-level approach. Whereas the grand-average approach (i.e., average across electrodes) is useful to observe the global tendency of the data, the sensor-level approach (the assessment of the behavior of each particular electrode and its spatial distribution) shows the spatial distribution of such tendencies. Only very slight statistically significant differences were found in SE in the comparison of HCs and MPs. These differences were localized at the right fronto-central and right parietal-occipital regions. Non–statistically significant differences were found after FDR correction for RP, MF, and IAF in the conventional EEG bands both for the comparison between HCs and MPs and for the comparison between the migraine CM and EM (see the Supplementary Data for figures and detailed description of these results).

Determining Frequencies of Interest in Migraine

The analysis of the conventional spectral bands and of the individual bands, as well as the broadband band, showed very slight or no significant differences. This motivated the FOI analysis in which specific frequency bands were determined to discriminate between groups. For that purpose, PSD_n was compared between groups. The PSD_n of HCs and MPs is depicted in Figure 1A. A zoom of the previous PSD_n is shown in Figure 1C, focused on the frequencies in which statistically significant

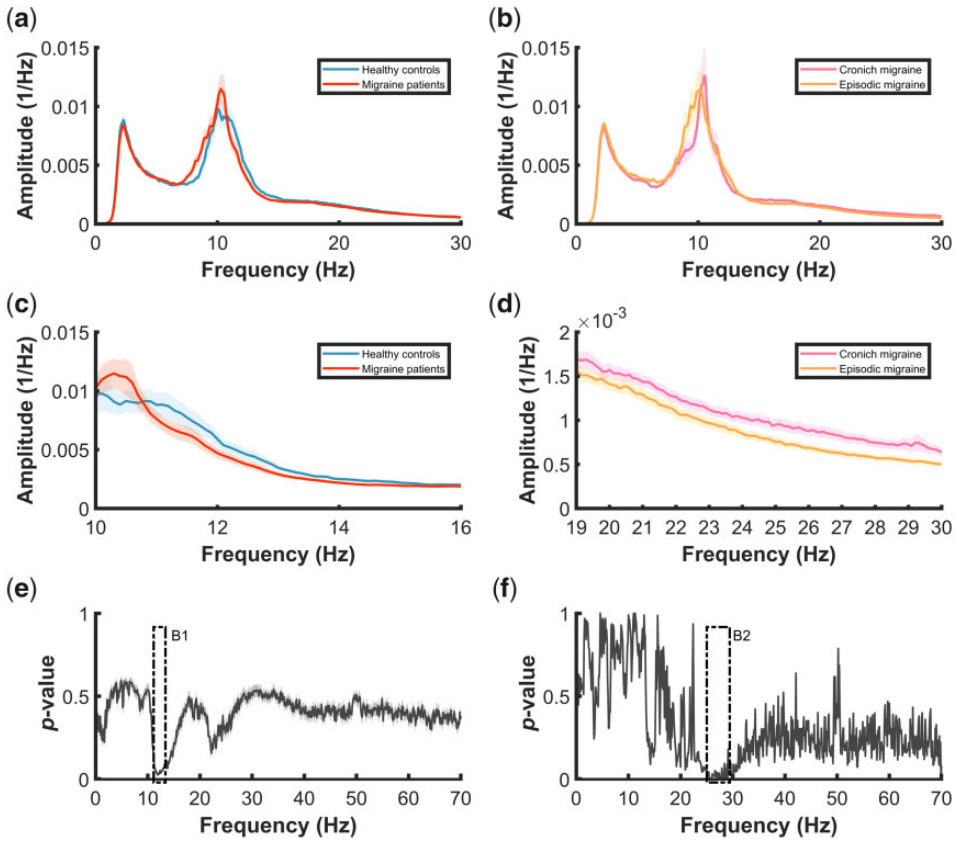

Figure 1. Normalized power spectral density (PSD_n) and frequencies of interest (FOIs). A) Averaged PSD_n (bold line) and 95% confidence interval (transparency) for healthy controls (HC) and migraine patients (MP). B) Averaged PSD_n (bold line) and 95% confidence interval (transparency) for episodic migraine (EM) and chronic migraine (CM). C) Zoom from (A) in the frequency range from 10 Hz to 16 Hz. D) Zoom from (B) in the frequency range from 19 Hz to 30 Hz. E) P values as a function of frequency for comparison between HC and MP determined by bootstrapping procedure after 1,000 iterations. The dashed line delimits the FOI, defined as $B1 \in [11.6, 12.8]$ Hz. D) P values as a function of frequency for the comparison between EM and CM, determined by bootstrapping procedure after 1,000 iterations. The dashed line delimits the FOI, defined as $B2 \in [24.1, 29.8]$ Hz.

differences after FDR correction were found (Figure 1E). On the other hand, PSD_n from EM and CM are represented in Figure 1B. As in the other comparison, a zoom of both PSD_n rates (Figure 1D) is shown in the frequency band where statistical differences after FDR correction were found between both groups (Figure 1F). Thus, two frequency bands were found: i) $B1 \in [11.6,\ 12.8]$ Hz for the comparison between HC and MP and ii) $B2 \in [24.1,\ 29.8]$ Hz for the comparison between EM and CM. Only these two frequency bands showed statistically significant differences.

To assess the specificity of the obtained FOIs, RP was computed in the frequency bands $B1$ and $B2$ to characterize HCs vs MPs and EM vs CM, respectively ($B1$ and $B2$). Figure 2 shows the grand-average distribution of the RP by means of violin plots and boxplots (Figure 2A). A statistically significant difference was observed between the HC and MP groups ($U = 3,087, P = 0.0013$). As expected, nonsignificant differences were obtained in the RP comparison between EM and CM ($U = 1,869$, $P = 0.4551$). In addition, Figure 2B depicts the topographical distribution of the RP in the $B1$ band for HCs and MPs, as well as the statistically significant differences after FDR correction. In the FOI $B2$, a significant difference was found in the RP grand-average distribution only between EM and CM ($U = 1,742, P = 0.0437$), as also shown in Figure 3A ($U = 1,742, P = 0.0437$). Spatial RP distribution and differences after FDR correction are depicted in Figure 3B.

Association Between EEG Characteristics and Migraine Duration

One of the hypotheses of the study is that the duration of the migraine has influence on specific EEG spectral characteristics. Nonetheless, it is not clear if the duration effect could be related to both groups of patients (EM and CM) or only to one of them. For that reason, we performed two independent analyses (one per group of patients) using the FOI with the property of discerning between groups (i.e., $B2$). All the performed correlations are reported in Table 2. Figure 4 shows the correlation

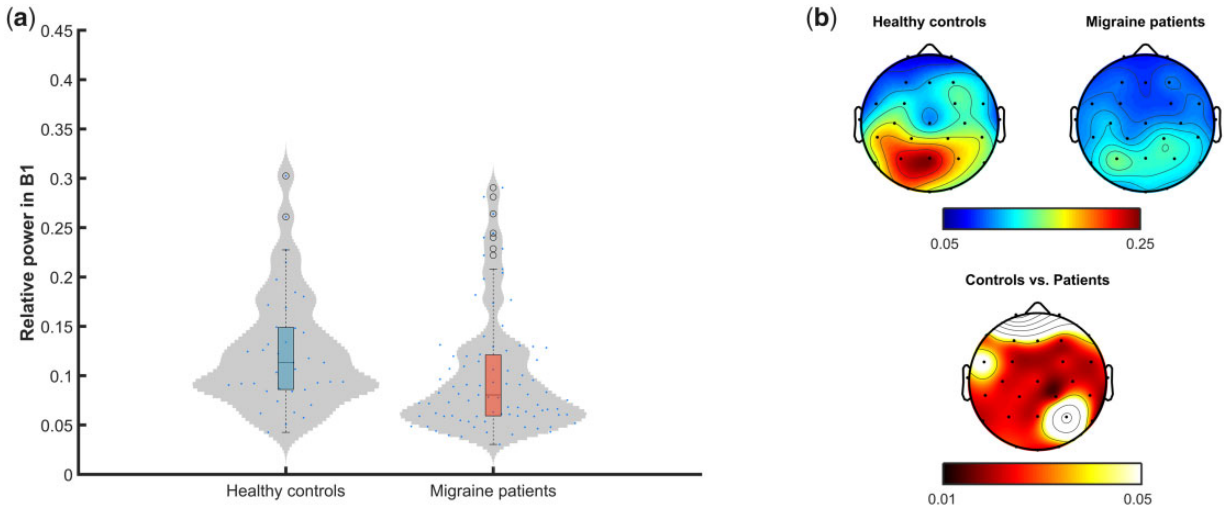

Figure 2. Spectral differences between healthy controls (HC) and migraine patients (MP). A) Boxplots and violin plots showing the distribution of the relative power (RP) in $B1\epsilon[11.2,\ 14.2]$ Hz ($P = 0.0008$). B) Spatial distribution of the relative power (RP) in $B1$ for HC and MP, as well as the statistical differences between them (false discovery rate–adjusted P values).

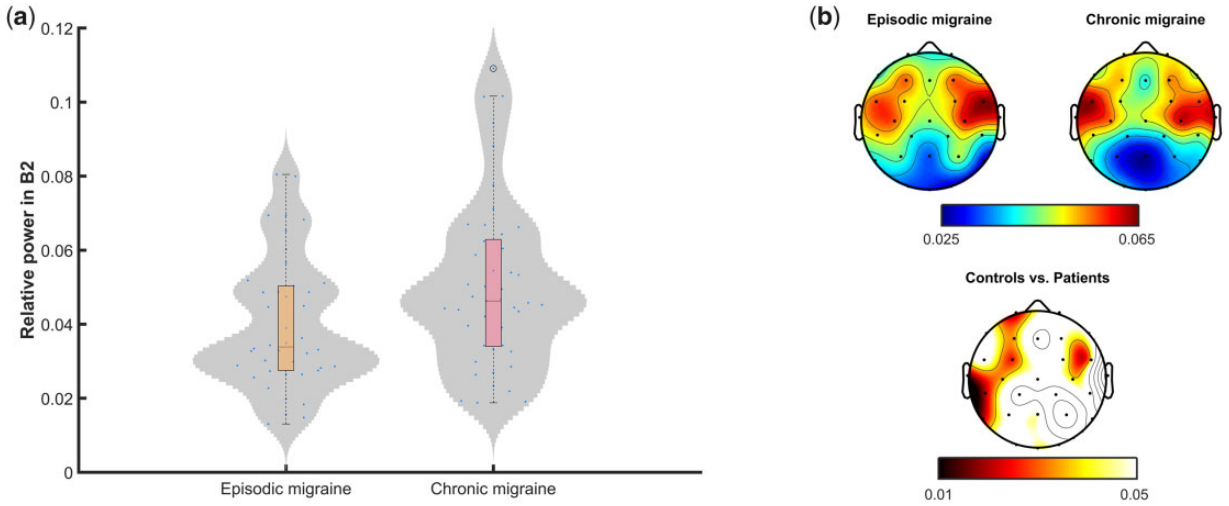

Figure 3. Spectral differences between episodic migraine (EM) and chronic migraine (CM). A) Boxplots and violin plots showing the distribution of the relative power (RP) in $B2\epsilon[23.4,\ 29.1]$Hz ($P = 0.0382$). B) Spatial distribution of the relative power (RP) in $B2$ for EM and CP, as well as the statistical differences between them (false discovery rate–adjusted P values).

between migraine duration and RP in $B2$ for both groups. Whereas the EM group shows a statistically significant correlation ($r = 0.3712, \mathrm{N} = 45, P = 0.0211$), no significant association was found for CM ($r = -0.1555$, $\mathrm{N} = 42, P = 0.2891$) or for all patients together ($r = 0.1281, \mathrm{N} = 87, P = 0.3109$). We repeated this procedure in patients without aura in order to remove possible bias due to this condition. In migraineurs without aura, the same patterns were found, that is, a statistically significant correlation for EM ($r = 0.3693, \mathrm{N} = 42$, $P = 0.0222$), as opposed to no association for CM ($r = -0.1325, \mathrm{N} = 39, P = 0.3541$). Similarly, we look for an association between total duration in chronic state (CM group) and RP in $B1$ and $B2$. In line with the result of total illness duration, no correlation was found for $B1$ ($r = -0.0341, \mathrm{N} = 42, P = 0.9002$) or $B2$ ($r = -0.0081$, $\mathrm{N} = 42, P = 0.9558$). All correlations were controlled for the effect of the age of the subjects.

Discussion

The Hyperexcitability and Hypoexcitability Dilemma in Migraine

Both hyperexcitability [24,25] and hypoexcitability [2] have been previously reported in migraine. The former has been described as a key factor in the interictal period of this illness [2]. On the contrary, a recent study found a global slowdown of the EEG signal and reduced photic responses during the interictal stage, which was linked to a hypoexcitability state in migraine [2]. Taking these findings together, one can conclude that this issue remains unresolved.

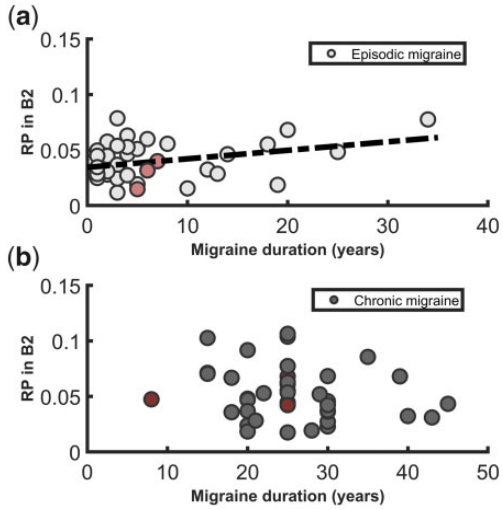

Figure 4. Correlations between spectral characteristics and migraine duration. A) Scatter plot and linear regression for episodic migraine (EM) group using relative power (RP) in $B2\epsilon[23.4,\ 29.1]$ Hz and migraine duration ($r = 0.3483$, $P = 0.0238$). B) Scatter plot for the CM group using RP in $B2$ and migraine duration ($r = -0.1762$, $P = 0.2768$). No linear regression was depicted in this case, as no significant correlation was found. For both graphics, subjects that suffered from headache with aura are highlighted.

Table 2. Results of the correlation analysis performed between spectral features (RP in $\beta 2$, MF, and IAF) and migraine duration

		RP ($\beta 2$)		MF		IAF	
	N	*P*	*r*	*P*	*r*	*P*	*r*
CM	42	0.2891	–0.1555	0.2114	–0.1739	0.0773	–0.2756
EM	45	**0.0211**	**0.3712**	0.3719	0.1046	0.2982	0.1881
MP	87	0.3109	0.1281	0.7512	–0.0944	0.9832	–0.0023

Both the *P* values and the correlation coefficient (Spearman's rho) are reported. Significant differences are highlighted in bold. All correlations were controlled for the effect of age of the subjects.

CM = chronic migraine; EM = episodic migraine; MP = migraine patients.

In this study, we try to shed light on this dilemma by indicating possible reasons for the aforementioned contradictory results. Different findings showed diminished power in low frequencies, such as delta and theta frequency bands [1], accompanied by an increased beta power [26] supporting the hyperexcitability hypothesis. However, using a larger database than many studies in this field, no statistical differences were found after FDR correction in the conventional EEG bands, neither in low frequencies nor in higher ones. This supports the fact that characteristic neural dynamics in migraine are linked to specific frequency bands, not necessarily equal to conventional ones. However, these findings must be taken with caution. Previous studies have shown EEG differences in migraine patients (specifically in episodic migraine) relative to controls [27]. The effects were more prominent during the eye-open condition compared with the eye-closed condition. Therefore, the lack of changes in the current study could be because the effects are not noticeable with the eyes closed. Future studies should be carried out to test it.

In this regard, after FOI analysis, MP was associated in this study with an important reduction of the relative power in β1 (from 11.6 Hz to 12.8 Hz), which is a particular sub-band in high alpha. This analysis reveals higher power in the parieto-occipital areas for HCs and MPs, which is expected for eye-closed acquisition during rest [28]. The distribution of the statistical differences was, however, spread all over the scalp (Figure 2). These results are in line with a previous study that reported anomalies in alpha in both hemispheres in migraine with aura [29]. In the same way, statistically significant differences between EM and CM in specific frequencies in high beta (i.e., in $B2$) reveal the importance of studying particular sub-bands. Comparison of the spatial distribution of the power spectrum between episodic and chronic migraineurs in β2 showed statistical differences mainly in fronto-central areas. Unfortunately, no previous studies have shown similar results, as they do not differentiate between EM and CM groups. Replication studies should be carried out in the future to reinforce this finding.

Based on the results of this study, we speculate that the result related to the excitability dilemma in migraine could have been hindered by a number of confounding factors. Interindividual variability is a crucial factor that can hide different characteristics in migraine disease, making necessary an FOI analysis to determine relevant frequency bands. In addition, the lack of consideration of migraine subgroups could also hide features due to the different behaviors of both groups in specific frequency bands.

The Role of Disease Duration

Besides the influence of subgroups in migraine and the importance of an FOI analysis, one of our primary findings was the role of illness duration in the EEG patterns. This study is one of the first in the literature reporting correlations between clinical features and EEG variables in migraine. Specifically, to the best of our knowledge, only one previous study has reported a correlation between spectral features of the EEG and illness duration [30]. However, Bjørk et al. [30] focused on alpha rhythms, leaving other waves unexplored until now. In that study, a negative correlation was found between illness duration and the alpha peak frequency (i.e., IAF) during the interictal phase of migraine. The authors suggest that subclinical ischemic events could be linked with posterior cerebral circulation in migraine [30,31].

In the present study, we did not find such a correlation in MP between IAF and illness duration ($r = -0.0023, \mathrm{N} = 87, P = 0.9832$) or for EM ($r = 0.1881, \mathrm{N} = 42, P = 0.2982$) (Table 2). However, a weak association (and no statistical significance for this statistical power) seems to exist for CM

($r = -0.2756, \mathrm{N} = 45, P = 0.0773$). Based on this result, we hypothesized that most of the subjects in the study of Bjørk et al. [30] were chronic patients, and therefore a significant negative association was obtained. This finding reinforces the fact that merging EM and CM groups can hinder some important conclusions.

In addition, a statistically significant correlation between RP in a particular band around high beta ($B2$) and duration of migraine history was found (Table 2). However, this significant but weak correlation was only shown for the EM subgroup ($r = 0.3712$). No correlation was revealed for the CM group, which presents significantly longer disease duration compared with the EM group (Table 1). Although it is not possible to infer a causal relationship using simple correlations, it is possible to recognize a trend in the data showing a significant correlation between illness duration and the background activity of the EEG, which in turn is linked to migraine subgroups. This led us to speculate that the spectral effects of the migraine are prone to be strongly manifested at the beginning of the illness, in which EM is more likely. Over the years, once the disease stabilizes, the EEG spectral characteristics are less variable—the reason for the lack of association with CM. This is also supported by the lack of association with CM between duration in chronic state and RP in $B1$ and $B2$.

Limitations

This study has limitations. First, we only assessed the interictal phase of migraine, a time interval in which no migraine attack could influence the results. Therefore, the results can only be linked to subclinical manifestations, as patients did not exhibit symptoms during the recording. Several studies found an important association between migraine cycle and electrophysiological underpinnings [2,30]. Further studies must explore the differences between EM and CM in specific frequencies, but in different migraine stages. This could provide relevant clues about the interindividual variance in migraine. Third, a control group was used to determine specific frequency bands of the EEG in which migraine patients show an abnormal behavior. Although non–statistically significant differences were found in age and sex between both groups, the group of healthy controls was half the size of the MP group. We avoided this issue using an approach based on bootstrapping. However, further efforts must be considered in the future in order to recruit a paired and large enough set of healthy controls. Last, but not least, conclusions about the role of illness duration must be made with care. Correlations do not provide causal inference, and, therefore, it is not possible to know if illness duration influences the EEG spectrum for EM patients, or if the right line of reasoning is exactly the contrary. Longitudinal studies assessing the time–frequency domain of the EEG in EM would be welcome.

Conclusions

We provided direct evidence of the capability of FOI analysis to ascertain the spectral characteristics of electrical brain activity in migraine during the interictal stage. Our results support the need to study not only the conventional frequency bands of the EEG, but also particular bands reflecting interindividual variability. In particular, we propose that i) the frequency band $B1\epsilon[11.2, 14.9]$ Hz may distinguish between healthy controls and patients with migraine and ii) the frequency band $B2\epsilon[26.1, 28.3]$ Hz may discriminate between episodic and chronic migraine. The spectral differences between migraine subtypes (EM and CM) imply that merging both groups can be a confounding factor that would hide important characteristics in migraine. Finally, a significant correlation between EEG power in high beta and illness duration was found in EM patients. It could reflect the relevance of illness duration in the type of treatment.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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