Clinical Neurophysiology Practice 4 (2019) 85–89

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

Research paper

Sex influences the frequency of the posterior basic alpha rhythm in patients with epilepsy

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ARTICLE INFO

Article history:
Received 12 January 2019
Received in revised form 8 April 2019
Accepted 8 April 2019
Available online 26 April 2019

Keywords:
EEG
Photic stimulation
Alpha frequency
Epilepsy
Anticonvulsants

ABSTRACT

Objective: To determine effects of sex, epilepsy and epilepsy medication on the posterior basic alpha rhythm.
Methods: We reviewed the routine EEGs of 160 subjects, including 60 individuals with focal epilepsy, 60 with generalized epilepsy, and 40 healthy controls, measured the mean alpha frequencies of each person and applied a univariate three-factorial analysis of variance.
Results: Women have a significantly faster posterior basic rhythm as compared to men. Sex was the only independent factor influencing the posterior basic rhythm in this cohort. Additionally, we detected an interaction with intake of lamotrigine and idiopathic generalized epilepsy both increasing the basic alpha frequency in the group of female subjects only.
Conclusion: Sex was the main determinant of the posterior basic alpha frequency in our cohort.
Significance: Sex can influence the frequency of the posterior basic alpha rhythm.

1. Introduction

Alpha waves are present in the EEG of the posterior head regions of relaxed, awake individuals with their eyes closed and have been proposed to be a correlate of cerebral mechanisms modulating sensory attention (Hanslmayr et al., 2011). Hans Berger coined the term alpha rhythm for the 10 Hz frequency which he discovered in the earliest electroencephalograms. Brazier and Finesinger (1944) defined the alpha rhythm as a frequency band based on a study of 500 healthy individuals whose mean frequency was 10.5 Hz with a standard deviation of 0.9. Thus, they defined the normal range as 8–13 Hz that is within 3 standard deviations from the population mean. Additionally, they observed that the dominant frequency of any one person is constant with only tiny fluctuations. Other authors similarly reported the individual alpha frequencies as a stable clinical marker over time in healthy persons (Grandy et al., 2013). On average, the dominant frequency increases in childhood until adolescence and again decreases especially with older age (Aurlien et al., 2004). Other factors influencing the posterior dominant alpha frequency may be mental tasks (Haegens et al., 2014), spontaneous variability (Khan et al., 2018), or older generation antiseizure medications (Veauthier et al., 2009). Based on the abundance of factors modulating the posterior dominant alpha frequency, our primary goal was to assess the effect of untreated epilepsy versus one treated with lamotrigine or valproate monotherapy on this biomarker.

2. Methods

2.1. Ethics

The study was approved by the local ethical committee and is in accordance with the declaration of Helsinki.

2.2. Subjects

We performed a retrospective search of our EEG database for routine EEGs performed with photic stimulation between April 2010 and February 2017. EEGs with photic stimulation were used, first, because of the shielded and automatized nature of the homogeneous sensory procedure of photic stimulation supposedly establishing a comparable level of alertness and second, because of the reliable trigger signals this procedure introduces into the EEG-data-file interindividually allowing robust and repetitive automatized detection of epochs with posterior dominant

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https://doi.org/10.1016/j.cnp.2019.04.002
2467-981X/

frequencies by a script programmed for this purpose. We found 1121 matches from which we extracted those of subjects who either 1) did not have epilepsy, or 2) had focal or generalized epilepsy but were currently not on antiseizure medications, or 3) had either focal or generalized epilepsy and were on monotherapy with lamotrigine or 4) were on monotherapy with valproate. The classification of the type of epilepsy was based on all patient data most notably anamnesis, semiology of seizures, EEG and neuroimaging if available. Group sizes of patients being on antiepileptic monotherapy other than lamotrigine or valproate were too small to be included into the analysis. The number of patients with focal and generalized epilepsy adhering to criteria two to four were equal. The EEGs were screened for significant abnormalities during photic stimulation, and those showing epileptiform activity or e.g. relevant slowing and asymmetry during photic stimulation were excluded from analysis as well as patients with occipital epilepsy. Likewise, subjects with significant comorbidities of the central nervous system were not included in this study. A total of 160 subjects between 18 and 73 years of age were selected for analysis. Classifying data of the subjects are summarized in Table 1. Eight of the 160 patients showed a background rhythm with a mixture of alpha and beta-frequencies (i.e. 11–25 Hz or 9–16 Hz). These patients were included into our analysis. Two patients, one control and one with epilepsy taking lamotrigine had predominantly beta frequencies in their normal posterior background activity (14–18 and 18–20 Hz). As there was remaining alpha-activity, we also included these patients into the analysis. There were no patients with a slow alpha variant in our cohort. Regarding potentially relevant medication effect, 4 patients were taking antidepressant medication and 14 patients were taking at least one antihypertensive drug. In 16 women, the intake of oral contraception was documented. However, in contrast to aforementioned concurrent medications, documentation of contraceptive medications may not have been as rigorous in the seven-year span of this retrospective study.

2.3. Technique

While being a retrospective study the electroencephalography is a fairly standardized procedure in our department of Clinical Neurophysiology. Typically, patients are recumbent with the upper body and head slightly elevated. The EEG electrodes are fixed according to the international 10–20 system with an 18-channel electroencephalograph recording for 20 min each (sampling frequency = 256 Hz, time constant = 0.1 s, electrode impedance <5 kΩ, XLTEK®-EEG acquisition machine). The experimental procedure for photic stimulation is as follows: Flashes of white flickering LED light were applied at frequencies of 3, 6, 9, 12, 15, 20, and 30 Hz. Application duration for each frequency is 20 s followed by ten seconds with no stimulation during which patients are asked to keep their eyes closed. We analyzed responses of the posterior electrodes O1 and O2, since these sites show the clearest alpha response. The reference electrode was Cz.

2.4. Design

The patients were stratified according to disease state and medication (Table 1). We created three groups: healthy controls, patients with focal epilepsy, and patients with generalized epilepsy, respectively. The groups of epilepsy patients were subdivided into those taking valproate (average dose 1002.5 ± 377.48 in patients with focal epilepsy and 1355 ± 512.19 mg in patients with generalized epilepsy), lamotrigine (average dose 273.68 ± 173.5 with focal epilepsy and 332.5 ± 186.57 mg with generalized epilepsy), or no medication. The latter group was composed mostly of patients with newly diagnosed epilepsy. EEGs had been performed on the control group subjects because of syncopal episodes that had been subsequently diagnosed as non-epileptic.

2.5. Spectrum analysis

The EEG data were analyzed and processed using the software Matlab® and CURRY 7®. The individual alpha frequency for each patient was calculated from those nine-second EEG epochs in the ten-second stimulation-free interval following a photic stimulation in which eyes remained closed. We excluded the first second after the end of each stimulation period to avoid carry-over effects or any photic driving response. A fast Fourier transform power spectrum was calculated, and the individual alpha frequency was defined as the frequency with the maximum absolute power in the 8 to 13 Hz frequency range. The maximum absolute power (μV^2) was calculated for each interval.

2.6. Statistics

Primarily, frequency and amplitude data were tested for normal distribution with the Kolmogorov-Smirnov test. If normal distribution was confirmed parametric tests were applied as indicated below. If testing demonstrated that data were not normally distributed we decided to perform a log transformation of the data. Thereafter, we again tested for normal distribution of these transformed version of the data and parametric tests were then applied if this testing indicated normal distribution.

We calculated the correlation between age and frequency, and age and amplitude using the Pearson and Spearman correlation coefficients, respectively. If the correlation with age was significant, age was included as a covariate in our analysis of variance (ANOVA) and was excluded in the opposite case. We then applied a three-way general linear model with the dependent variable "alpha frequency" as the mean of seven data sets (i.e. after photic stimulation with 3, 6, 9, 12, 15, 20, and 30 Hz) and the categorial factors "medication" with four categories of 40 subjects each (no

Table 1
N = number of subjects; Age given as median; N = no medication; L = lamotrigine, V = valproate.

Groups	Subgroups	N	Age	m/f	N/L/V
Medication	None – No Epilepsy	40	33.5	20/20	–
	None – Epilepsy	40	31	16/24	–
	Lamotrigine – Epilepsy	40	25	20/20	–
	Valproate – Epilepsy	40	30	26/14	–
Epilepsy	No Epilepsy	40	33.5	20/20	40/–/–
	Focal Epilepsy	60	35	30/30	20/20/20
	Generalized Epilepsy	60	26.5	32/28	20/20/20
Gender	Male (m)	82	27.5	–	36/20/26
	Female (f)	78	33.5	–	44/20/14
Total		160	29	82/78	80/40/40

medication in control patients, epilepsy patients with no medication, patients taking valproate, patients taking lamotrigine) and "disease" (no epilepsy, focal epilepsy, generalized epilepsy). Sex was included as an additional factor. Tukey's test was used for post-hoc testing. SPSS 24® for Microsoft Windows® and Microsoft Excel 2013® were used for statistical analysis, preparation of figures and graphs, and data management. Methods used for this study have been previously described in a companion investigation on variability of the alpha-rhythm in the same cohort (Khan et al., 2018).

3. Results

The Kolmogorov-Smirnoff test revealed that the frequency data were distributed normally. The mean alpha frequency of all study subjects was 10.24 ± 0.88 Hz. The Pearson correlation coefficient for the factors "age" and "mean alpha frequency" was −0.142 ($p = 0.074$), indicating only a trend towards alpha slowing with age. Hence, age was not included as covariate in our general linear model.

The Levene-test supported the Null-hypothesis that variances of our groups were comparable ($F(13, 146) = 1.1$; $p = 0.37$). Neither epilepsy ($F(1, 146) = 0.213$; $p = 0.645$) nor medication ($F(2, 146) = 2.413$; $p = 0.093$) were significant main factors in the three way general linear model on effects on posterior alpha frequency. However, the alpha rhythm of the 78 female subjects was significantly faster (10.46 ± 0.87 Hz) than that of the 82 male subjects (10.04 ± 0.84 Hz) ($F(1, 146) = 9.066$; $p = 0.003$) (Fig. 1). Between-subject analysis furthermore revealed weak but significant interactions between sex and medication ($F(2, 146) = 3.188$; $p = 0.044$) as well as a three-term-interaction between sex, medication and epilepsy ($F(2, 146) = 3.213$; $p = 0.043$) (Fig. 2). *Post-hoc* testing demonstrated that the mean alpha frequency of patients taking lamotrigine (10.53 ± 0.9 Hz) was significantly faster than in the healthy control group (10.01 ± 0.83 Hz; $p = 0.024$) as well as in the group of patients taking valproate (10.02 ± 0.84 Hz; $p = 0.028$) a finding that held true in the female group only (female patients taking lamotrigine ($n = 20$; 10.99 ± 0.82 Hz), valproate ($n = 14$; 10.08 ± 0.77 Hz; $p = 0.011$), healthy control group ($n = 20$; 10.2 ± 0.93 Hz; $p = 0.015$)). Female patients with idiopathic generalized epilepsy taking lamotrigine had the overall highest posterior basic alpha frequency ($n = 13$; 11.06 ± 0.76 Hz).

Fig. 1. Diagram demonstrating the relation between sex and mean value of the posterior dominant alpha frequency in Hertz. Bars indicate the confidence interval.

Amplitudes of the posterior alpha rhythm (mean 10.47 ± 13.87 μV^2) were not normally distributed (Kolmogorov-Smirnov test, $p < 0.001$). After log-transformation (corresponding mean 1.25 ± 1.55) we applied an ANOVA. Neither medication, epilepsy, nor sex had any influence on amplitude.

4. Discussion

4.1. Frequency of the posterior alpha rhythm

The average alpha frequency of 10.24 ± 0.88 Hz in all groups is in line with the reported mean values in young, healthy adults (Lindsley, 1936; Brazier and Finesinger, 1944; Koyama et al., 1997; Aurlien et al., 2004) indicating representativeness of our cohort. The posterior basic rhythm in women robustly was nearly 0.5 Hz faster than that in men in our cohort. While some previous studies have not found a sex-difference regarding alpha-frequency (Brazier and Finesinger, 1944; Hawkes and Prescott, 1973) such a difference has also been found in a large cohort of more than 4500 subjects, in which EEG interpretation was based on visual inspection and was detected approximately from age 15 onwards increasing with age (Aurlien et al., 2004). The same study also demonstrated a generally greater amplitude of the alpha rhythm in females, which supports some previous results (Wang and Busse, 1969) while contradicting others (Petersen and Eeg-Olofsson, 1971). Our study may not have had sufficient power to detect an amplitude difference in the alpha frequency band. The frequency of the posterior basic alpha rhythm of women in the luteal phase of their menstrual cycle is 0.1–0.5 Hz faster than that of women in the follicular phase (Dusser de Barenne and Gibbs 1942; Brötzner et al., 2014) which corresponds to different blood levels of progesterone and estradiol, respectively. Statistically seen, the phase of the menstrual cycle is an unlikely cause of the difference in mean alpha frequency in our study. On the other hand, data on the effect of oral contraceptives on the alpha rhythm are more heterogeneous (Brötzner et al., 2014; Wuttke et al., 1975). The 16 women in our cohort in whom intake of oral contraceptives was documented had a mean alpha frequency of 10.24 ± 0.93 Hz which matches the average of the whole cohort (10.24 ± 0.88 Hz). Nevertheless, documentation of contraception may have been less stringent than that of other medications raising the possibility that more than 16 women were receiving contraception. Moreover, the type of the oral contraceptive was not consistently detailed. Nonetheless, given the rather young mean age of our female subjects (33.8 ± 13.6 years of age) fertility-related physiological mechanisms may have been more pronounced than in a cohort with a higher age on average. Additionally, a positive relationship has been established between EEG frequency and body temperature (Gundel, 1984; Thompson and Harding, 1968), which is generally higher in women. In contradistinction to other authors who claim that "sex differences are minor compared to [quantitative] EEG changes associated with aging" (Veldhuizen et al., 1993), we found a significant sex effect. This suggests an important role of sexual hormones on the alpha rhythm, although the exact mechanisms of this difference remain unclear.

Lack of a significant effect of age on alpha frequency in our cohort is most likely the consequence of the underrepresentation of older age groups (9 subjects over 60) due to the general avoidance of photic stimulation in persons older than 65 as well as the lack of subjects younger than 18 years of age in our study. Hence, our data are systematically biased towards adults of young to mid age. In fact, a decrease in alpha frequency and power with increasing age has, with some exceptions (Koyama et al., 1997), been a robust finding in comparable studies (Mundy-Castle et al., 1954; Obrist 1954). For healthy controls a successive decrease

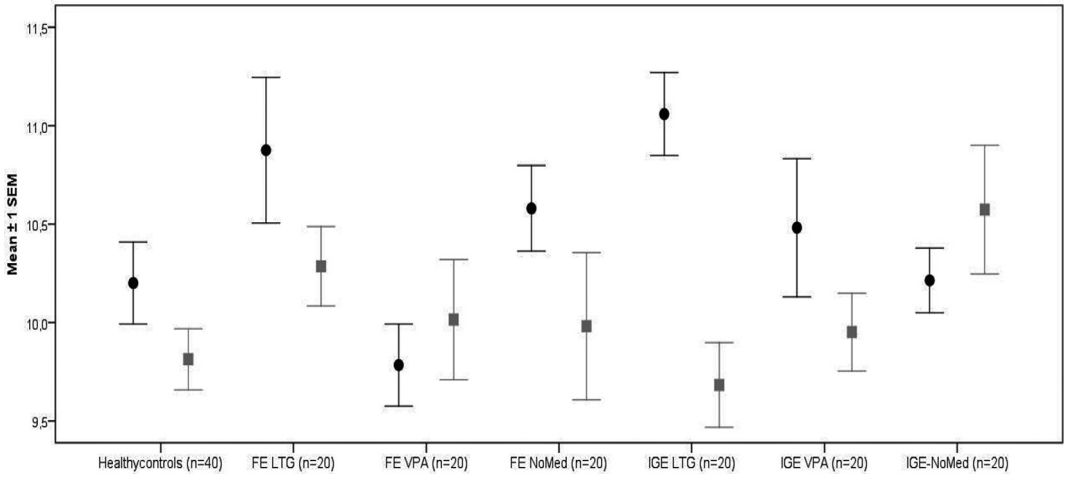

Fig. 2. Diagram detailing the interaction between sex and medication as well as epilepsy. FE = focal epilepsy, IGE = idiopathic generalized epilepsy, LTG = lamotrigine, VPA = valproate; SEM = standard error of the mean. Black bars with circles indicate data from female subjects, grey bars with squares indicate data from male subjects.

from 9.7 Hz in the 60-year-old age group, to a mean of 9.4 Hz with an average age of 75 years to 9.0 Hz in 90-year-old subjects is reported (Berger, 1932; Mundy-Castle et al., 1954; Obrist and Busse 1965). And, in a large database analysis of alpha rhythm in more than 4500 EEGs the mean alpha rhythm started to decrease from age 45 onwards (Aurlien et al., 2004). Hence, our results suggest that the well-known decrease of the frequency of the posterior basic rhythm with age becomes significant later in life and is less relevant in the age groups investigated in our study.

There was no main effect of "epilepsy" on posterior alpha-rhythm. Previous studies that reported alpha changes in epilepsy had difficulties in accounting for the role of medications as a cofactor. In a study comparing 18 patients with either focal (n = 10) or generalized (n = 8) epilepsy with a non-epilepsy control group (n = 10) the mean alpha frequency was lower in the epilepsy group (9.4 Hz vs. 10.3 Hz in the occipital leads) (Larsson and Kostov, 2005). However, the patients were not all receiving the same anti-seizure medications. Larger samples of patients with epilepsy off anticonvulsive medication may be necessary to detect possible disease inherent deviations of average background frequencies. Interestingly, in our group of female patients, lamotrigine significantly accelerated the posterior dominant alpha frequency (Clemens et al., 2006). Others have not found any significant effect of lamotrigine on the posterior dominant alpha frequency (Marciani et al., 1996). Still, the latter study included only patients with intractable epilepsy receiving polytherapy, thus limiting solid conclusions. Our study has a number of limitations, including the inability to address a number of potential confounding factors. While the role of age, for example, could not be assessed adequately due to the limited range of age included, other factors such as the role of cognitive state, weight and sensorimotor processing were not studied owing to the retrospective nature of this study. And with respect to our main finding of a sex difference of the alpha frequency, this study does not provide accurate registration of possibly relevant factors for this difference including type and frequency of contraceptive methods or phase of the menstrual cycle of the female subjects.

In conclusion, foremost sex significantly influences parameters of the posterior alpha rhythm in patients with epilepsy.

Acknowledgements

We thank Christoph Anten (Department of Medical Statistics, University Medical Center Göttingen) for evaluation of and contribution to the statistical methods of the manuscript. Furthermore, we would like to thank Prof. Dr. T. Crozier for the helpful proofreading of and commenting on the manuscript.

Conflict of interest

All authors declared to have no conflict of interests related to this work.

Source of funding

This project has been supported by an intramural grant of the University Medical Center Göttingen.

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