



Abnormal visual sensitivity in eyelid myoclonia with absences: Evidence from electrocortical connectivity and non-linear quantitative analysis of EEG signal



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ABSTRACT

Purpose: Eyelid myoclonia with absences (EMA) is an epileptic syndrome characterized by eyelid myoclonia with or without absences, eyes closure-induced EEG paroxysms and photosensitivity. Pathophysiological mechanisms of visual sensitivity in EMA are not-fully understood. The objective of the present study was to analyze the electrophysiological dynamics implicated in the visual sensitivity in patients with EMA.

Methods: We analyzed data of 10 subjects with diagnosis of EMA and of 10 healthy control subjects. For both patients and controls, 4-seconds artifacts-free electroencephalographic signal epochs recorded were analyzed, during resting state, eyes-opened and eyes-closed tasks. Resting state networks in EEG have been computed using independent components analysis (ICA) LORETA. Moreover, the power law exponent β was obtained for each coordinate as minus the slope of the power spectrum versus frequency in a Log-Log scale.

Results: Using LORETA ICA, patients during resting state showed significant differences as compared to controls with a reduction of the physiological alpha activity over the occipital lobe and of the physiological beta activity over the frontal lobe. Immediately after eye closure, a significant increase of beta activity over the frontal lobe was found in the group of patients compared to controls. Power law exponent β analysis showed a significant increase of β over the frontal regions in patients as compared to controls during resting-state and an increase of β over the parieto-occipital regions after eye closure.

Conclusion: Abnormal occipital and frontal cortex activities seem to be related with the visual sensitivity and eyelid myoclonia observed in patients with EMA.

1. Introduction

Eyelid myoclonia with absences (EMA) is an epileptic syndrome characterized by a well-defined clinical and electroencephalographic (EEG) phenotype: eyelid myoclonia with or without absences, eyes closure-induced EEG paroxysms and photosensitivity [1].

As for other Idiopathic Generalized Epilepsies (IGE), recently re-named as Genetic Generalized Epilepsies (GGEs), in EMA a high prevalence of positive family history for epilepsy has been found, leading to the hypothesis of a genetic etiology [1–3]. One of the genes strictly related to the syndrome is CHD2, a gene associated with different phenotypes but particularly linked with epilepsy and photosensitivity [4,5].

Photosensitivity, defined as an abnormal cortical response to

flickering light, related to electroencephalography changes and associated or not with seizures [5], is considered one of the main triggering factors of seizures in EMA, and the recent genetic discoveries confirm its role as a distinctive and genetically determined feature of the syndrome. Bright light is the most important precipitating factor in EMA. EEG recordings in EMA typically reveal high voltage generalized spike and wave discharges 0.5–2 s after eye closure in illuminated place [6], while eye closure in darkness does not induce any effect.

Neurophysiologic studies both on animal models and humans, demonstrated that the occipital and fronto-rolandic cortex as well as the brainstem are the main areas involved in photosensitive epilepsy [7,8]. A recent study with EEG-correlated functional magnetic resonance imaging (EEG-fMRI) and voxel-based morphometry (VBM) demonstrated an increased Blood-Oxygen-Level-Dependent (BOLD) signal in

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the occipital cortex of subjects with EMA after eye closure, confirming the role of an abnormal occipital cortex activity in generating discharges that propagate to the fronto-rolandic cortex where the eyelid myoclonus is probably generated [9,10]. Moreover, very recent findings seem to support the hypothesis that the networks generating the alpha activity at rest could be intrinsically altered in patients with epilepsy and visual sensitivity, with a decrease of the alpha-related inhibition of the visual cortex and sensory-motor networks [11].

Despite the few referred observations, pathophysiological mechanisms implicated in visual sensitivity in EMA remain not-fully understood.

LORETA (Low Resolution Brain Electromagnetic Tomography) is a method by which the non-invasive measurement of electrical potentials carried out by EEG can be used to estimate the connectivity of neuronal electrical activity. Moreover, non-linear quantitative EEG method could also be relevant to analyse cortical activities. Differently from linear methods of analysis, such as the spectral analysis, which assume that analyzed signals are temporally stationary and their variations harmonic in nature, a non-linear approach based on the relationship between signal frequency and amplitude may give additional information on how EEG signal is modulated over time and thus if it follows a random or deterministic behavior. A non-linear quantitative analysis of the EEG signal through the calculation of the power law exponent β , which is minus the slope of the power spectrum versus frequency in a Log-Log scale, has shown to be appropriate for describing complexity of electrocortical activity [12,13]. The power law exponent β describes how signal is modulated over the frequency spectrum, representing a quantitative estimation of signal complexity [14]. This information may have important clinical implications since changes in β values have been also detected in EEG signals of animal models during the transition between pre-seizure to seizure stage [15].

Therefore, based on the previous findings of an involvement of occipital and fronto-rolandic cortex in patients with EMA [9–11] and considering the inverse relationship between frequency and exponent β values [14], we hypothesize to disclose consistent alterations of the electrocortical networks underlying the dysfunctional occipital-frontal visuomotor pathway in EMA patients.

The main objective of the present study was to analyze, by means of low resolution electromagnetic tomography (LORETA) and EEG quantitative analysis with a nonlinear methodology, the electrocortical networks possibly implicated in the visual sensitivity and in the eyelid myoclonus in a group of patients with EMA.

2. Methods

2.1. Study population

We analyzed data of $N = 10$ subjects with EMA for whom a diagnosis of Jeavons syndrome was made according to the following criteria: occurrence of eyelid myoclonia, with or without absences, related to EEG generalized epileptiform activity and triggered by eye closure; generalized photoparoxysmal EEG response, often in combination with a history of visually induced seizures and photosensitivity [1]. We also selected $N = 10$ healthy control subjects with normal electroencephalography for whom the diagnosis of epilepsy was excluded.

All the study subjects have undergone standardized electroencephalography as part of their diagnostic work-up at the time of their visit to our Neurological Center. A written informed consent was obtained from study participants.

2.2. EEG recordings

For each subject in the group of patients, the first EEG recording performed in our center was selected while, for control subjects, any of their EEG recordings was analyzed. For both patients and controls, 4-seconds artifacts-free electroencephalographic signal epochs recorded

from 19 electrodes placed according to the 10–20 system (Fp2, F4, C4, P4, O2, F8, T4, T6, Fz, Cz, Pz, Fp1, F3, C3, P3, O1, F7, T3, T5) with unipolar derivation and common reference (G2) using a pre-cabled headcap were analyzed, during resting state (relaxed eyes-closed wakefulness), eyes-opened and eyes-closed tasks (SystemPLUS ver. 1.02.1109 for BRAIN-QUICK BQ132 S, Micromed). In particular, regarding the eyes-closed task, 4-seconds artifacts-free epochs immediately after the eye closure artifact were selected. Five different samples for each site and state were selected.

Final visual control of the selected epochs was carried out by an expert electroencephalographer (LG) in order to ensure the quality of the samples. EEG impedances were kept between 2 and 10 k Ω at the homologous sites. Signals were band-pass filtered (1.6–30 Hz) and NOTCH filtered. Sampling rate was 256 Hz for all the recordings.

2.3. LORETA analysis

Time series of cortical electric neuronal activity estimated with LORETA can be used to estimate cortical networks and connectivity [16]. LORETA is a method to localize multiple distributed cortical sources of bioelectric activity in the three-dimensional space [17]. Resting state networks in EEG have been computed using independent components analysis (ICA) LORETA, based on the assumption that the brain areas and frequencies in a network always activate together. A standardized LORETA (sLORETA) resting state network normally consists of many images of electric cortical activity, one for each frequency [18,19]. In the present study the following frequency bands were considered: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz) and beta (13–30 Hz) during resting state, eyes-opened and eyes-closed tasks.

The output of LORETA analysis was a tomographically arranged series of color-coded pictures displaying the algebraic difference and the statistical difference between the two groups of EMA and controls. Localization was given in anatomical terms, specifying the lobe, the gyrus and the Brodmann area of the abnormality [17].

2.4. EEG quantitative analysis and exponent β computation

A Welch's periodogram (50% overlap between 1-s Hamming windowed segments) was applied to 4-seconds artifacts-free electroencephalographic signal epochs recorded from specific homologous pairs of electrodes over each hemisphere (F3/4, F7/8, T3/4, P3/4, O1/2) based on standardized protocol [20]. The Power Spectral Density [PSD (mV²/Hz)] of sampled signal epochs during resting state, eyes-opened and eyes-closed tasks over each homologous site was computed for each selected frequency band (delta, theta, alpha and beta).

Then, the power law exponent β was obtained for each coordinate as minus the slope of the power spectrum versus frequency in a Log-Log scale, to estimate self-similarity of the detected electrocortical signal. Self-similarity is a property of dynamic processes that can be evaluated by analyzing the presence of a power law relationship between frequency and size of the process variation [21,22]. For β values ~ 0 , the process is considered stationary, a sequence of time-ordered uncorrelated random variables (“white noise”). β values ~ 1 imply self-similarity, typical property of fractal phenomena. β values ~ 2 indicate a process tending to the Brown noise also called “random walk”, represented by the sum of random shocks [21,22]. More specific details on this nonlinear methodology have been provided elsewhere [20].

Test-retest reliability of β was analyzed before performing any statistical inference, based on the different epochs sampled during resting state. The Intraclass Correlation Coefficient demonstrated high reliability of β over each site of recordings ranging from 0.93 to 0.98 over the different sites.

2.5. Statistics

Qualitative variables were described as frequencies and

percentages, while quantitative variables as mean \pm standard deviation (SD). The data were examined for normality using Shapiro-Wilk test. To analyze differences between groups, the independent samples *t*-test has been applied for parametric data, while the Mann-Whitney test was used for non-parametric data. To analyze differences within groups between two activation states (resting state *versus* the eyes-closed task), the paired samples *t*-test has been applied for parametric data, while the Wilcoxon signed rank test has been applied for non-parametric data.

For LORETA analysis, voxel-wise LORETA group comparison included calculating simple algebraic differences between the groups in order to demonstrate all differences. Statistically significant differences were generated in a second phase. Student-*t* test for independent groups was carried out to compare patient versus control datasets. Student *t*-test for paired data was performed when comparing different tasks in the same group.

3. Results

A total number of 10 patients [3 men (30%); mean age 24.5 \pm 15.9 years] and 10 controls [6 men (60%); mean age 23.1 \pm 6.5 years] were enrolled. All patients were treated with AEDs but only three patients were seizure-free at the time of the enrollment. Clinical characteristics of the group of patients are shown in Table 1.

3.1. LORETA analysis

Regarding the analysis of the resting state, significant differences were found between patients and controls with a reduction of the physiological alpha activity over the occipital lobe (lingual gyrus, Brodmann area 17) and of the physiological beta activity over the frontal lobe (middle frontal gyrus, Brodmann area 11) in the group of patients. Moreover, an increase of alpha activity was found among patients in a network involving the parietal lobe (precuneus, Brodmann area 7) (Fig. 1).

Regarding the eyes-closed task, a significant increase of beta activity over the frontal lobe (inferior frontal gyrus, Brodmann area 47) was found in the group of patients compared to controls immediately after eye closure (Fig. 1D).

During the eyes-opened task, no significant differences were found between patients and controls.

Comparing the different tasks in the group of patients (Fig. 2) we found significant differences between the resting state and the eyes-closed task in the group of patients with a decrease of alpha activity in a network involving the occipital lobe (fusiform gyrus, Brodmann area 18) and an increase of alpha and beta activities over the frontal lobe

Table 1
Clinical features of 10 patients with Eyelid myoclonia with absences.

Variables	N (%)
Age at onset in years (mean \pm SD)	12 \pm 4.1
Family history of epilepsy (n)	3 (30)
Psychomotor delay (n)	1 (10)
Comorbidities (n)	1 [†] (10)
Precipitating factors	3 (30)
Stress (n)	3 (30)
Sleep deprivation (n)	2 (20)
Menstrual cycle (n)	
Photosensitivity	9 (90)
Mean follow-up time in years (mean \pm SD)	9 \pm 4.9
AEDs	9 (90)
Valproic Acid (n)	3 (30)
Levetiracetam (n)	1 (10)
Lamotrigine (n)	1 (10)
Phenobarbital (n)	
Seizure freedom (n)	3 (30)

N, number; SD, standard deviation; AEDs; antiepileptic drugs.

[†] phenylketonuria.

(superior frontal gyrus, Brodmann area 11) during eye closure. When comparing eyes-opened and eyes-closed task in patients, a significant increase of beta activity over the frontal lobe and decrease of alpha activity over the occipital lobe was found in patients during eye closure. Furthermore, in the group of patients, when comparing the eyes-opened task with the resting state, a physiological reduction of alpha activity over the occipital lobe (lingual gyrus, Brodmann area 18) and an increase of beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 6) was found.

In the control group (Fig. 3), significant differences were found between resting state and eyes-closed task with a decrease of both alpha activity over the occipital lobe (cuneus, Brodmann area 19) and beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 11) after eye closure. A physiological reduction of beta and alpha activity over the frontal lobe (superior frontal gyrus, Brodmann area 11 and middle frontal gyrus, Brodmann area 11) and an increase of alpha activity over the occipital lobe (cuneus, Brodmann area 19) was found in patients during eye closure compared to the eyes-opened task. Moreover, when comparing the eyes-opened task with the resting state, a physiological reduction of alpha activity over the occipital lobe (lingual gyrus, Brodmann area 18) and an increase of alpha and beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 10) was found in the control group.

3.2. Power law exponent β analysis

Comparing the values of β over the different brain areas between patients and controls, we found a significant increase of β over the frontal regions in the group of patients during the resting state (Fig. 4 and Supplement 1). No differences were found between the two groups during eyes-closed and eyes-opened tasks

Moreover, in the group of patients, significant differences were found between the resting state and the eyes-closed task with an increase of β over the parieto-occipital regions after eye closure (P3, $p = 0.03$; P4, $p = 0.0005$; O1, $p = 0.001$; O2, $p = 0.0006$) (Fig. 4). Similar differences between the two states were not found in the group of controls.

4. Discussion

A network is defined as “a functionally and anatomically connected, bilaterally represented, set of cortical and subcortical brain structures and regions in which activity in any part affects activity in all the others” [23]. In the last years, different studies have been carried out with the aim of exploring the cortical and subcortical brain networks and their abnormalities in various neurological diseases. Epilepsy and, above of all, GGEs are probably the best models to study the alterations of these networks, being considered as network disorders. Most of the studies performed until now, aimed to explore the functional networks involved in the generation of seizures in GGE, have been focused on how both ictal epileptiform activity and interictal epileptiform discharges can be linked to the presence of pathological brain networks [24–26]. Moreover, a common endophenotype has been identified among GGE patients, suggesting an intrinsic alteration of the brain connectivity not only in these patients but also in their family members [27–32].

Until now, only few studies have explored the networks involved in photosensitivity and, even less works have been focused on the brain correlates of visual sensitivity in patients with EMA, all suggesting that both phenomena can be the expression of an alteration of the visual system, not limited to the occipital cortex, but involving a more extended functional network. [9,11,29]. In particular, a very recent study found that photosensitivity could be linked to an alteration of cortical-subcortical networks generating the alpha rhythm [11].

Aim of our study was to evaluate the electrocortical correlations of the wider “visual sensitivity phenomenon” including both

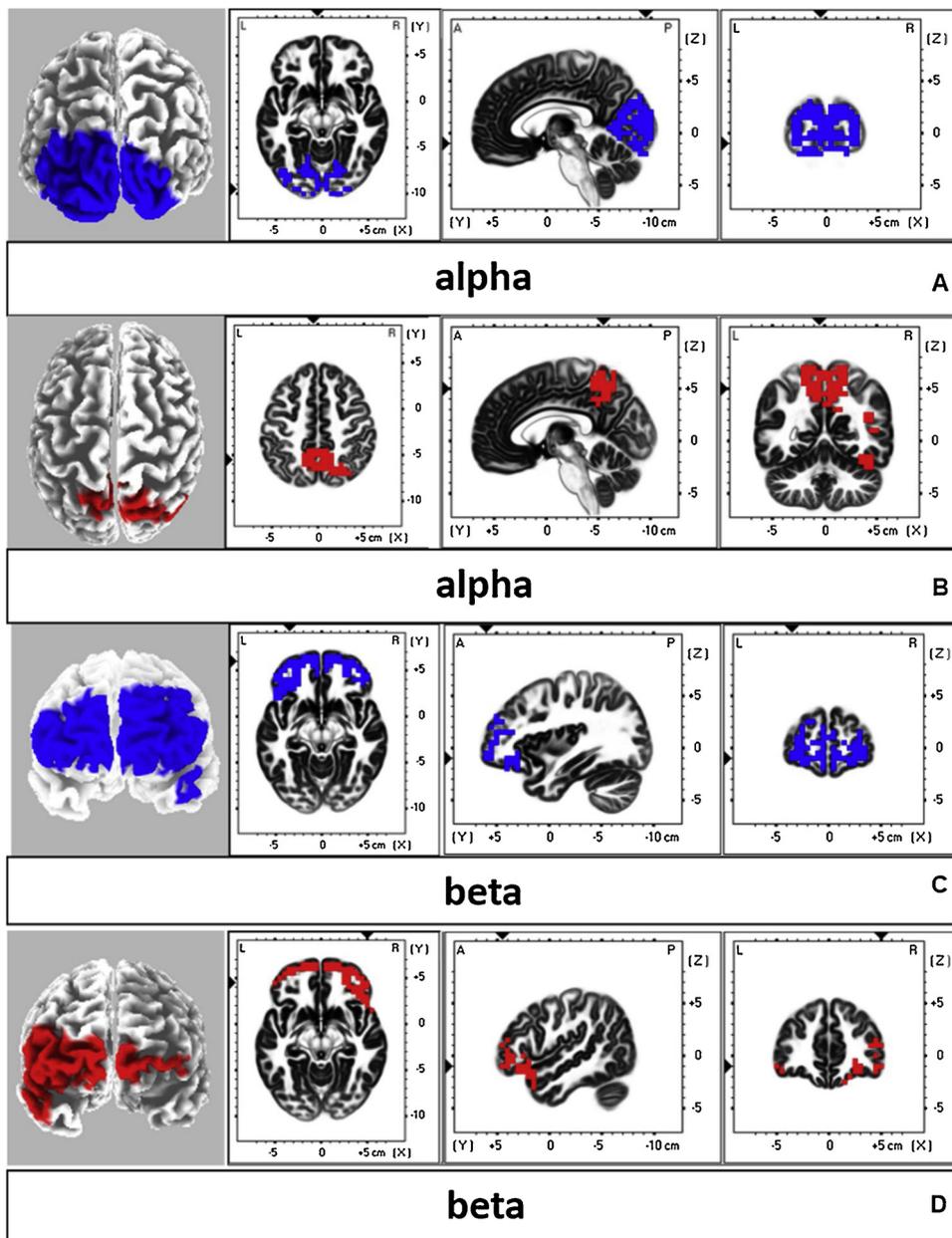


Fig. 1. Comparison between patients and controls using LORETA Independent Component Analysis (ICA). **A.** reduction (blue) of the physiological alpha activity over the occipital lobe (lingual gyrus, Brodmann area 17) in the group of patients compared to controls during resting state. **B.** increase (red) of alpha activity in a network involving the parietal lobe (precuneus, Brodmann area 7) in patients compared to controls during resting state. **C.** reduction of the physiological beta activity over the frontal lobe (middle frontal gyrus, Brodmann area 11) in the group of patients compared to controls during resting state. **D.** immediately after the eye closure increase of beta activity over the frontal lobe (inferior frontal gyrus, Brodmann area 47) in the group of patients compared to controls during the eyes-closed task (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

photosensitivity and eye closure sensitivity, typical hallmarks of EMA syndrome, by the use of different methodologies.

The findings of our study can be summarized as follows: during resting state, we confirmed the hypothesis of a decreased network within the alpha frequency over the occipital lobes in EMA patients, with the presence of decreased networks within the beta frequency linked with an increase of exponent β over the frontal lobes in EMA patients, in the range of random processes. Moreover, differences were found in the group of patients among the three tested states with a gradient leading to a higher alteration of occipital alpha activity and increased frontal beta activity when passing from resting state to eyes-opened and finally to eyes-closed, associated with an increase of exponent β over the parieto-occipital regions after eye closure. A similar gradient, characterized by the highest level of frontal activation and background activity disorganization during the eye closure task, was not found in the group of controls.

In fact, during the resting state, the networks analysis in patients with EMA, performed by means of independent component analysis (ICA) LORETA revealed a significant reduction of the physiological

alpha activity over the occipital lobe in patients with EMA. This finding seems to be in line with previous demonstrations of an increased BOLD signal over the occipital cortex which is known to be correlated with decreased alpha activity in these areas [9]. It is in fact well known that an increased alpha activity is found in inhibited cortical areas while lower alpha activity can be found in activated areas, as those involved in the visual hyper-excitability of EMA patients [33]. However, we did not find a significant alteration of exponent β values over the occipital areas during resting state, maybe due to the physiological behavior of this index, which is usually higher over the occipital areas also in normal subjects. Due to the power law relationship between signal frequency and amplitude, β is in fact expected to be higher for low frequencies with high signal amplitude modulation, such as for the occipital alpha activity. Moreover, we found a reduction of the physiological beta activity over the frontal areas in EMA patients compared to controls. This datum can be partially explained by the demonstrated presence of an increased coupling between posterior and anterior areas in subjects with photosensitivity, indirectly confirming the role of an abnormal occipital cortex in the onset of reflex seizures and of the

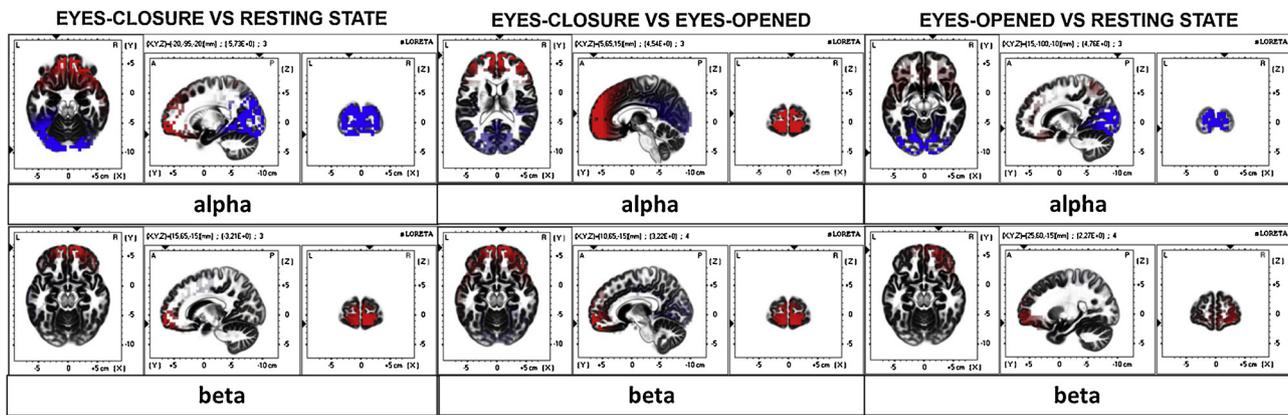


Fig. 2. Intragroup comparison in the group of EMA patients using LORETA Independent Component Analysis (ICA). *On the left:* after eye closure compared to the resting state significant decrease (blue) of alpha activity over the occipital lobe (fusiform gyrus, Brodmann area 18) with an increase (red) of alpha and beta activities over the frontal lobe (superior frontal gyrus, Brodmann area 11). *On the middle:* during the eyes-closed task compared to the eyes-opened task significant increase of alpha and beta activities over the frontal lobe (superior frontal gyrus, Brodmann area 11) with a decrease of alpha activity over the occipital lobe (lingual gyrus, Brodmann area 18). *On the right:* during the eyes-opened task compared to the resting state significant decrease of alpha activity over the occipital lobe (lingual gyrus, Brodmann area 18) with an increase of beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 6) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

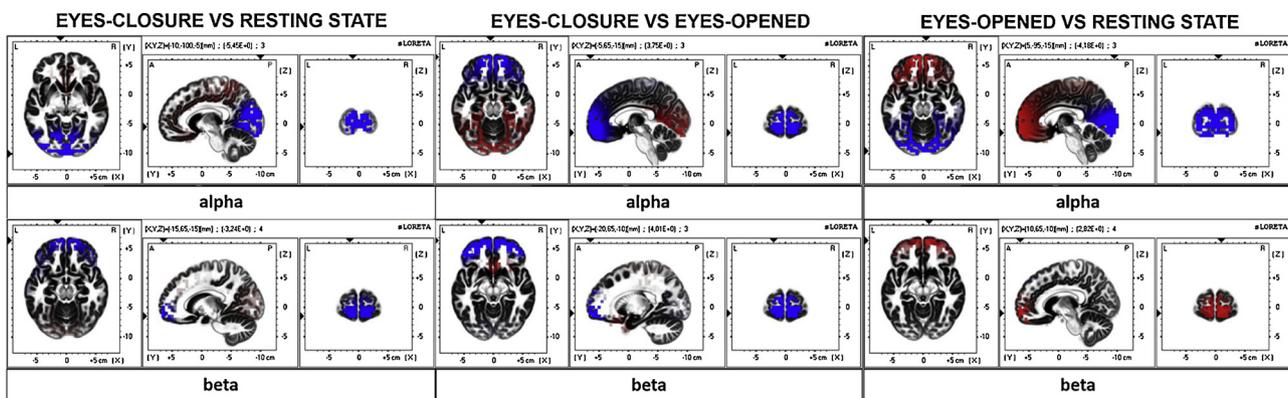


Fig. 3. Intragroup comparison in the group of controls using LORETA Independent Component Analysis (ICA). *On the left:* after eye closure compared to the resting state significant decrease (blue) of both alpha activity over the occipital lobe (cuneus, Brodmann area 19) and beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 11). *On the middle:* after eye closure compared to the eyes-opened task significant increase (red) of alpha activity over the occipital lobe (cuneus, Brodmann area 19) and decrease of alpha and beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 11). *On the right:* during the eyes-opened task compared to the resting state significant decrease of alpha activity over the occipital lobe (lingual gyrus, Brodmann area 18) with an increase of alpha and beta activity over the frontal lobe (superior frontal gyrus, Brodmann area 10) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

fronto-rolandic cortex in generating the epileptiform discharges and eyelid myoclonus [10].

Moreover, we found in our patients immediately after the eye closure, an increased representation of a network involving beta activity over the frontal areas, coupled with an increase of exponent β over the parieto-occipital regions, both findings potentially linked to the intrinsic pathological occipital-frontal network that has its higher expression after the closure of the eyes in EMA patients [9]. The increase of β is in fact index of a chaotic activity induced by the eye closure over the visual cortex, temporally correlated with a pathological increase of desynchronization over the frontal areas, possibly related to the motor manifestations of photo-induced seizures. Therefore, it is not surprising the discovery of an increased exponent β over the frontal regions in this group of patients at rest, sign of an altered, random process from which seizures may arise [15]. On the other hand, the presence of an increased alpha activity among patients in a network involving the parietal lobe confirms the previous data of a negative correlation between alpha rhythm and brain activity in different areas such as the parietal lobule and specifically the precuneus. In fact, a previous study revealed, immediately after the eye closure, decrements of the BOLD signal in the posterior areas of the default mode network (DMN), in particular the

precuneus and bilateral inferior parietal lobuli, possibly reflecting the brief awareness impairment during the absences in EMA [9].

However, it cannot be ruled out the effect of AEDs in the group of patients, mainly regarding the representation of slow frequencies in various brain regions. In fact, contradictory influences of different AEDs have been found on electrocortical activity [34–37].

Nonetheless, despite the small sample size of our study, this is to our knowledge the first study exploring the neurophysiological characteristics of a homogeneous group of patients with EMA. Our well-selected study population is in fact representative of the described cohorts of EMA patients present in the literature [1,10,38,39], presenting a mean age at onset during childhood or adolescence, a large percentage of positive family history for epilepsy, the presence of a subgroup of subjects with psychomotor delay and the high rate of drug resistance.

5. Conclusions

In conclusion, even if the exact nature of visual sensitivity in patients with EMA remains unclear and many different pathogenetic hypotheses can be made, the findings of our study confirm the existence of an altered occipital-frontal electrocortical network in these patients.

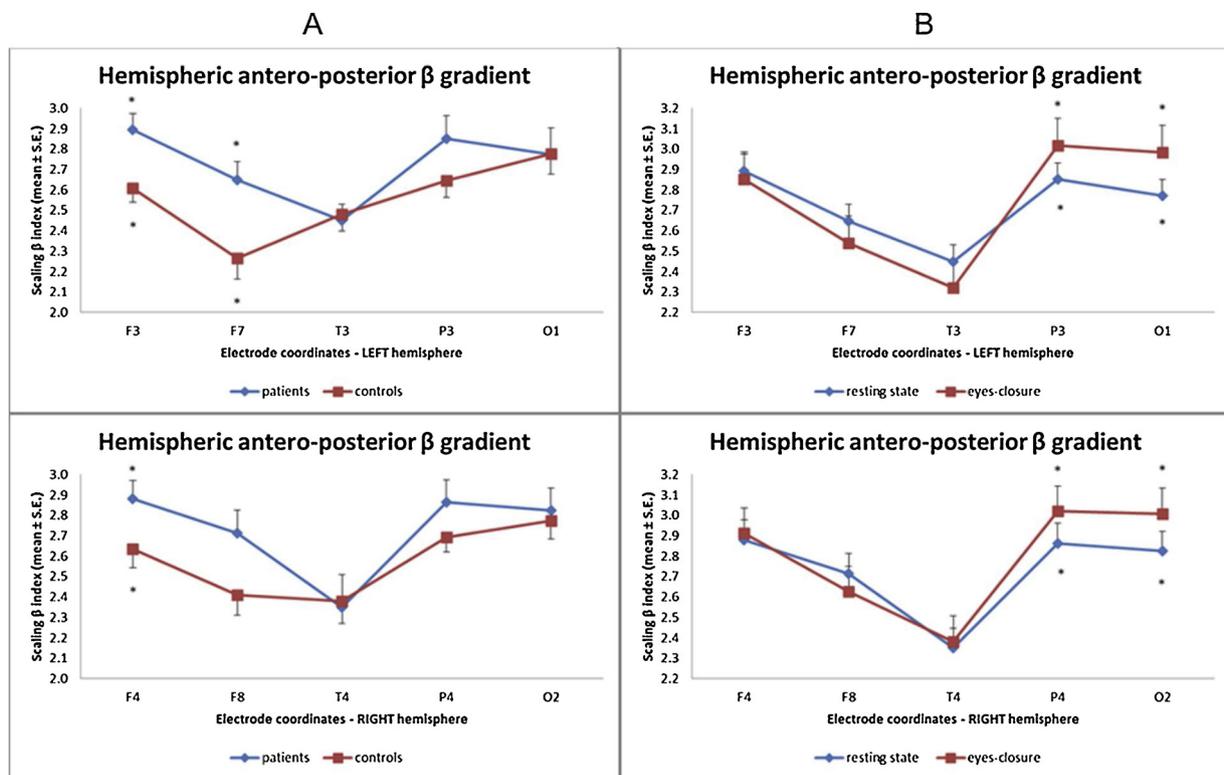


Fig. 4. Values of the power law exponent β in patients and controls and in patients during different states. A. differences in the values of exponent β between patients and controls during the resting state over the left (upper) and right hemisphere (lower). B. differences in the values of exponent β in the group of patients (B) between the resting state and the eyes-closed task over the left (upper B) and right hemisphere (lower B).

* $p < 0.05$

Moreover, our data, showing a significant reduction of the physiological alpha activity over the occipital lobe in patients with EMA, confirmed the previous evidence of a dysfunctional alpha rhythm in generating photosensitivity in EMA.

Declarations of interest

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Transparency document

The Transparency document associated with this article can be found in the online version.

References

- Panayiotopoulos CP. Syndromes of idiopathic generalized epilepsies not recognized by the International League Against Epilepsy. *Epilepsia* 2005;46(Suppl 9):57–66. <https://doi.org/10.1111/j.1528-1167.2005.00314.x>.
- Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia* 2017;58:522–30. <https://doi.org/10.1111/epi.13670>.
- Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia* 2017;58:512–21. <https://doi.org/10.1111/epi.13709>.
- Galizia EC, Myers CT, Leu C, de Kovel CGF, Afrikanova T, et al. CHD2 variants are a risk factor for photosensitivity in epilepsy. *Brain J Neurol* 2015;138:1198–207. <https://doi.org/10.1093/brain/awv052>.
- Sosa RG, Nangia S. Photosensitivity and CHD2 Variants. *Pediatr Neurol Briefs* 2015;29:66. <https://doi.org/10.15844/pedneurbriefs-29-9-1>.
- Giannakodimos S, Panayiotopoulos CP. Eyelid myoclonia with absences in adults: a clinical and video-EEG study. *Epilepsia* 1996;37:36–44.
- Artieda J, Obeso JA. The pathophysiology and pharmacology of photic cortical reflex myoclonus. *Ann Neurol* 1993;34:175–84. <https://doi.org/10.1002/ana.410340213>.
- Naquet R, Silva-Barrat C, Menini C. Reflex epilepsy in the Papio-papio baboon, particularly photosensitive epilepsy. *Ital J Neurol Sci* 1995;16:119–25.
- Vaudano AE, Ruggieri A, Tondelli M, Avanzini P, Benuzzi F, Gessaroli G, et al. The visual system in eyelid myoclonia with absences. *Ann Neurol* 2014;76:412–27. <https://doi.org/10.1002/ana.24236>.
- Striano S, Capovilla G, Sofia V, Romeo A, Rubboli G, Striano P, et al. Eyelid myoclonia with absences (Jeavons syndrome): a well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions? *Epilepsia* 2009;50(Suppl 5):15–9. <https://doi.org/10.1111/j.1528-1167.2009.02114.x>.
- Vaudano AE, Ruggieri A, Avanzini P, Gessaroli G, Cantalupo G, Coppola A, et al. Photosensitive epilepsy is associated with reduced inhibition of alpha rhythm generating networks. *Brain* 2017;140:981–97. <https://doi.org/10.1093/brain/awx009>.
- Pritchard WS. The brain in fractal time: 1/f-like power spectrum scaling of the human electroencephalogram. *Int J Neurosci* 1992;66:119–29.
- Pereda E, Gamundi A, Rial R, González J. Non-linear behaviour of human EEG: fractal exponent versus correlation dimension in awake and sleep stages. *Neurosci Lett* 1998;250:91–4.
- Stadnitski T. Measuring fractality. *Front Physiol* 2012;3:127. <https://doi.org/10.3389/fphys.2012.00127>.
- Li X, Polygiannakis J, Kapisir P, Peratzakis A, Eftaxias K, Yao X. Fractal spectral analysis of pre-epileptic seizures in terms of criticality. *J Neural Eng* 2005;2:11–6. <https://doi.org/10.1088/1741-2560/2/2/002>.
- Worsley KJ, Chen J-I, Lerch J, Evans AC. Comparing functional connectivity via thresholding correlations and singular value decomposition. *Philos Trans R Soc Lond B Biol Sci* 2005;360:913–20. <https://doi.org/10.1098/rstb.2005.1637>.
- Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int J Psychophysiol* 1994;18:49–65.
- Pascual-Marqui RD, Biscay-Lirio RJ. Interaction patterns of brain activity across space, time and frequency. Part I: methods. *ArXiv11032852 Math Q-Bio Stat [Internet]*. 2011 Available at: <http://arxiv.org/abs/1103.2852>. Accessed October 09, 2018.
- Pascual-Marqui RD, Kochi K, Lehmann D, Koukoku M, Kinoshita T. Functional independent components: revealing cortico-cortical, cross-frequency interactions. *Japanese J Pharm -EEG* 2011;12:53–8.
- Mostile G, Nicoletti A, Dibilio V, Luca A, Pappalardo I, Giuliano L, et al.

- Electroencephalographic lateralization, clinical correlates and pharmacological response in untreated Parkinson's disease. *Parkinsonism Relat Disord* 2015;21:948–53. <https://doi.org/10.1016/j.parkreldis.2015.06.006>.
- [21] Hausdorff JM, Peng CK, Ladin Z, Wei JY, Goldberger AL. Is walking a random walk? Evidence for long-range correlations in stride interval of human gait. *J Appl Physiol* 1985;1995(78):349–58.
- [22] Hausdorff JM, Purdon PL, Peng CK, Ladin Z, Wei JY, Goldberger AL. Fractal dynamics of human gait: stability of long-range correlations in stride interval fluctuations. *J Appl Physiol* 1985;1996(80):1448–57.
- [23] Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia* 2002;43:219–27.
- [24] Lee C, Im C-H, Koo YS, Lim J-A, Kim T-J, Byun J-I, et al. Altered network characteristics of spike-wave discharges in juvenile myoclonic epilepsy. *Clin EEG Neurosci* 2017;48:111–7. <https://doi.org/10.1177/1550059415621831>.
- [25] Benuzzi F, Ballotta D, Mirandola L, Ruggieri A, Vaudano AE, Zucchelli M, et al. An EEG-fMRI study on the termination of generalized spike-and-wave discharges in absence epilepsy. *PLoS One* 2015;10:e0130943 <https://doi.org/10.1371/journal.pone.0130943>.
- [26] Pugnaghi M, Carmichael DW, Vaudano AE, Chaudhary UJ, Benuzzi F, Di Bonaventura C, et al. Generalized spike and waves: effect of discharge duration on brain networks as revealed by BOLD fMRI. *Brain Topogr* 2014;27:123–37. <https://doi.org/10.1007/s10548-013-0311-0>.
- [27] Schmidt H, Woldman W, Goodfellow M, Chowdhury FA, Koutroumanidis M, Jewell S, et al. A computational biomarker of idiopathic generalized epilepsy from resting state EEG. *Epilepsia* 2016;57. <https://doi.org/10.1111/epi.13481>. e200–4.
- [28] Wei H, An J, Shen H, Zeng L-L, Qiu S, Hu D. Altered effective connectivity among core neurocognitive networks in idiopathic generalized epilepsy: an fMRI evidence. *Front Hum Neurosci* 2016;10:447. <https://doi.org/10.3389/fnhum.2016.00447>.
- [29] Liu F, Wang Y, Li M, Wang W, Li R, Zhang Z, et al. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Hum Brain Mapp* 2017;38:957–73. <https://doi.org/10.1002/hbm.23430>.
- [30] Clemens B, Puskás S, Besenyei M, Emri M, Spisák T, Koselák M, et al. EEG functional connectivity of the intrahemispheric cortico-cortical network of idiopathic generalized epilepsy. *Epilepsy Res* 2011;96:11–23. <https://doi.org/10.1016/j.eplepsyres.2011.04.011>.
- [31] Clemens B, Puskás S, Besenyei M, Emri M, Opposits G, Kis SA, et al. EEG-LORETA endophenotypes of the common idiopathic generalized epilepsy syndromes. *Epilepsy Res* 2012;99:281–92. <https://doi.org/10.1016/j.eplepsyres.2011.12.008>.
- [32] Chowdhury FA, Woldman W, FitzGerald THB, Elwes RDC, Nashef L, Terry JR, et al. Revealing a brain network endophenotype in families with idiopathic generalised epilepsy. *PLoS One* 2014;9:e110136 <https://doi.org/10.1371/journal.pone.0110136>.
- [33] Toscani M, Marzi T, Righi S, Viggiano MP, Baldassi S. Alpha waves: a neural signature of visual suppression. *Exp Brain Res* 2010;207:213–9. <https://doi.org/10.1007/s00221-010-2444-7>.
- [34] Béla C, Mónika B, Márton T, István K. Valproate selectively reduces EEG activity in anterior parts of the cortex in patients with idiopathic generalized epilepsy. A low resolution electromagnetic tomography (LORETA) study. *Epilepsy Res* 2007;75:186–91. <https://doi.org/10.1016/j.eplepsyres.2007.06.009>.
- [35] Clemens B, Puskás S, Besenyei M, Kovács NZ, Spisák T, Kis SA, et al. Valproate treatment normalizes EEG functional connectivity in successfully treated idiopathic generalized epilepsy patients. *Epilepsy Res* 2014;108:1896–903. <https://doi.org/10.1016/j.eplepsyres.2014.09.032>.
- [36] Clemens B, Piros P, Besenyei M, Tóth M, Hollódy K, Kondákor I. Imaging the cortical effect of lamotrigine in patients with idiopathic generalized epilepsy: a low-resolution electromagnetic tomography (LORETA) study. *Epilepsy Res* 2008;81:204–10. <https://doi.org/10.1016/j.eplepsyres.2008.06.002>.
- [37] Clemens B, Piros P, Besenyei M, Hollódy K. Lamotrigine decreases EEG synchronization in a use-dependent manner in patients with idiopathic generalized epilepsy. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2007;118:910–7. <https://doi.org/10.1016/j.clinph.2006.11.016>.
- [38] Capovilla G, Striano P, Gambardella A, Beccaria F, Hirsch E, Casellato S, et al. Eyelid fluttering, typical EEG pattern, and impaired intellectual function: a homogeneous epileptic condition among the patients presenting with eyelid myoclonia. *Epilepsia* 2009;50:1536–41. <https://doi.org/10.1111/j.1528-1167.2008.02002.x>.
- [39] Caraballo RH, Fontana E, Darra F, Chacon S, Ross N, Fiorini E, et al. A study of 63 cases with eyelid myoclonia with or without absences: type of seizure or an epileptic syndrome? *Seizure* 2009;18:440–5. <https://doi.org/10.1016/j.seizure.2009.04.004>.