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Research Paper

Circadian rhythm and sleep in focal epilepsy

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ABSTRACT

Although a relationship between sleep, circadian rhythm and the occurrence of epileptic seizures was first postulated over a hundred years ago, few studies, mainly with a small number of seizures were published.

In this study we analyzed all partial seizures determined by continuous EEG-monitoring to reevaluate previous results and to provide a first step towards creating chronotypes in epilepsy.

Data were collected at the epilepsy monitoring unit of the Department of Neurology, LMU University Hospital in Munich from 715 patients undergoing pre-surgical long-term Video-EEG-monitoring. Only seizures with a single focal seizure onset zone were considered and were divided into five groups: frontal, temporal, parietal, occipital and central region.

A total of 3950 seizures were included in the final analysis (temporal: 2055; frontal: 1512; central: 181; parietal: 90; occipital: 112).

Cosinor analysis revealed a periodicity in the occurrence of seizures regarding the temporal ($p = 0.019$), occipital ($p = 0.045$) und frontal lobe ($p = 0.034$) whereas parietal and central region seizures did not show a 24 h periodicity.

Temporal lobe seizures showed a peak at 10 am, whereas frontal lobe seizures peaked at 4 am and occipital lobe seizures at 4 pm.

Most seizures occurred in the awake state (in total 64.56 %) regardless of the seizure onset zone.

By knowing the peaks of seizure occurrence chronotypes can be identified and antiseizure medication can be adjusted accordingly. This might help to enhance seizure control and reduce seizure associated risk.

1. Introduction

A relationship between sleep, circadian rhythms and the occurrence of epileptic seizures was recognized early in the clinical description of epilepsies [8]. Subsequent studies specified the results for some epilepsy syndromes such as an occurrence of myoclonic seizures in Juvenile Myoclonic Epilepsy mostly after awakening [14] or an afternoon peak in mesial temporal lobe epilepsy [17]. In animal models, light-entrained rats exhibit more limbic seizures during the light period, and continue that time peak when brought to constant darkness [16]. The pathophysiology behind this relationship of circadian rhythm and the occurrence of seizures is still vague, with various factors such as a low melatonin, adenosine or cortisol level being considered [3].

Another highly debated issue is the impact of sleep on the occurrence of seizures. It's widely acknowledged that most seizures occur during sleep [9,10]. Even without nocturnal seizures, many epilepsy patients report sleep disturbances which can impair seizure control [2,6].

Studies analyzing the temporal occurrence of seizures with seizure onset zones other than mesiotemperal and frontal are rare and normally encompass only a few patients.

Hence, we analyzed all partial seizures determined by continuous EEG-monitoring to reevaluate former results and to add new information regarding rare seizure onset zones. Our study hypothesized that the circadian rhythm of seizure onset would differ between seizure onset regions. Furthermore, the impact of wakefulness on the occurrence of seizures and on the occurrence of focal to bilateral tonic-clonic seizures (= FBTCS) was analyzed.

2. Methods

2.1. Subject selection

Data were collected at the epilepsy monitoring unit at the Neurology department of LMU University Hospital between 2006 and 2019.

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For occipital lobe epilepsy, we analyzed all seizures between 2006–2023, since we saw a trend but not a statistically significant result in the initial cosinor analysis of the seizures between 2006 and 2019.

The localization of each patient's epileptogenic region was based on a thorough discussion in the epilepsy case conference. Patients without clear localization to one region only were not included. Further exclusion criteria were: non-epileptic diagnosis, multifocal or generalized epilepsy, multifocal seizure onset. Clinical seizures without an EEG change or status epilepticus were also excluded in the analysis.

Clinicoelectrographic seizures and electrographic only seizures (subclinical seizures) were included in the analysis as well as up to ten seizures per patient per recording and up to three seizures per day per patient (Supplementary Material, Table 1).

Data collection methods for this retrospective study were approved by the Ethics Board of the LMU University Hospital.

2.2. Seizure detection

Patients underwent continuous video and scalp-EEG-Monitoring (=EVM) for several days (range 3–18 days, median 9.34 days, standard deviation 2.84 days) using the 10–10 electrode placement system.

Antiseizure medication (= ASM) was tapered at the beginning of the recording. In most cases, ASM was withdrawn completely on the first day. Only patients with a history of status epilepticus were gradually weaned off.

Seizures were reviewed by at least two experienced epileptologists independently. If the results differed, these seizures were excluded from analysis, to ensure unambiguous data. Sleep was scored from the EEG in the minutes before the seizure, the seizure was considered to arise from sleep when a seizure pattern was visible directly from sleep or within 10 s after arousal onset, and when sleep had been present for at least 30 s before the seizure, corresponding with the definition of a sleep epoch length. As patients in EVM typically don't have electrooculography or electromyography available, we relied on the 10–10 EEG dataset to follow the AASM-criteria for sleep. All EEG patterns for sleep are well represented on the full EEG set and eye-movements are very well represented in the temporal lateral leads, allowing approximation of sleep scoring. Only the loss of muscle tone for scoring REM-sleep might be underscored, but seizures only very rarely arise from REM-sleep (Supplementary Material, Figure 1).

The following information was recorded for each seizure: 1) seizure type 2) region of onset 3) time of seizure onset 4) sleep/wake state at seizure onset.

2.3. Data analysis

Only seizures with a clear focal seizure onset were taken into consideration. Generalized seizures or seizures with a seizure onset zone in two or more lobes were excluded. To avoid any clustering bias, a maximum of three seizures per patient per day were considered. Seizures within the setting of a status epilepticus were excluded. The data was divided into 5 groups according to the seizure onset zone: temporal, frontal, parietal, and occipital lobe and the central region. The latter was defined as all seizures arising from the precentral and postcentral gyri. Anatomically, there are four lobes, but in epilepsy, the central region is typically differentiated as a separate zone because of its distinct connectivity and difficult surgical treatment (Supplementary Material, Figure 2).

Temporal distribution was assessed by binning the seizure frequency first in one-hour, then three-hour groups for each brain region. The first seizure of each patient was analyzed separately as well as well as the effect of sleep on the occurrence of seizures and FBTCS.

A cosinor analysis was utilized to model seizure occurrence over a 24-hour interval. Cosinor analysis uses a least squares method to fit a cosine wave to a time series data set. Plots of seizure occurrences were created according to the different seizure onset zones to visualize whether the cosinor model would fit the data as well as zero-amplitude tests were performed [13].

Peak time, peak time error and the 95th confidence limits were analyzed to determine whether there is a significant difference between the peak time of the different seizure onset zones (Welch-T-test).

In categoric variables, the Chi-square or Fisher's exact test was used to determine significant differences (whereas in continuous variables, Student's T-Test was used). A p-value of less than 0.05 was considered significant, a Bonferroni-Holm-correction was performed, and no statistically significant result had to be revoked.

3. Results

3.1. Overview of results

In total, 715 patients were screened for this study. 275 patients were excluded since they didn't meet the inclusion criteria. 3950 seizures of 440 patients were included in the final analysis (average of 8.98 seizure per patient, standard deviation 2.60). Regarding the seizure onset zone, 2055 seizures originated from the temporal lobe (52.04 %), 1512 from the frontal lobe (38.26 %), 181 from the central region (4.58 %), 90 from the parietal lobe (2.28 %) and 112 from the occipital lobe (2.84 %) (Supplementary Material, Figure 1).

3.2. Cosinor analysis

The cosinor analysis revealed a periodicity in the occurrence of seizures regarding the temporal ($p = 0.019$), occipital ($p = 0.045$) and frontal lobe ($p = 0.034$). Seizures from the temporal lobe showed a peak at 10am, whereas seizures from the frontal lobe peaked at 4am and seizures from the occipital lobe at 4 pm.

For seizures arising from the parietal lobe ($p = 0.723$) or central region ($p = 0.339$), data did not fit the model of cosinor analysis. Seizures from the parietal lobe showed a peak at 6am, central region seizures showed an increase of occurrence of seizures during the night with a nadir at 11am (Fig. 1).

3.3. First seizure

The occurrence of the first seizure was analyzed separately for each region. Only in seizures from the occipital lobe the data fit to a cosinor analysis ($p = 0.019$).

Seizures arising from the occipital lobe showed no difference between the first seizure compared to all seizures (Fig. 2). All other seizures showed a shift in occurrence during afternoon hours when only the first seizure was analyzed.

3.4. Acrophase analysis and 95th confidence limits of acrophase

The acrophase, peak time error estimate and 95th confidence limits of peak time were analyzed separately for each region and for all seizures and for the first seizures.

There was no overlap in the confidence limits of the peak time of all seizures between the different subgroups (temporal: acrophase (in hours) = 10.53; CI (in hours) = [9.41 to 11.65], frontal: acrophase = 4.24; CI = [3.42 to 5.06], central: acrophase = 23.21; CI = [20.88 to 1.54] (limits overlap), parietal: acrophase = 5.93; CI = [4.48 to 7.39], occipital: acrophase = 18.74; CI = [17.65–19.83]). P-value was < 0.01 except for the comparison between frontal and parietal, here the p-value was 0.045. Visually, both confidence limits overlap, but in the statistical analysis there was a significant difference (Supplementary Material Table 2).

The same statistical analysis was carried out for the first seizures. Here, the confidence limits of the peak time of the cosinor analysis of the temporal versus central ($p = 0.62$), temporal versus parietal ($p = 0.56$), frontal versus parietal ($p = 0.07$), frontal versus occipital ($p = 0.75$) and

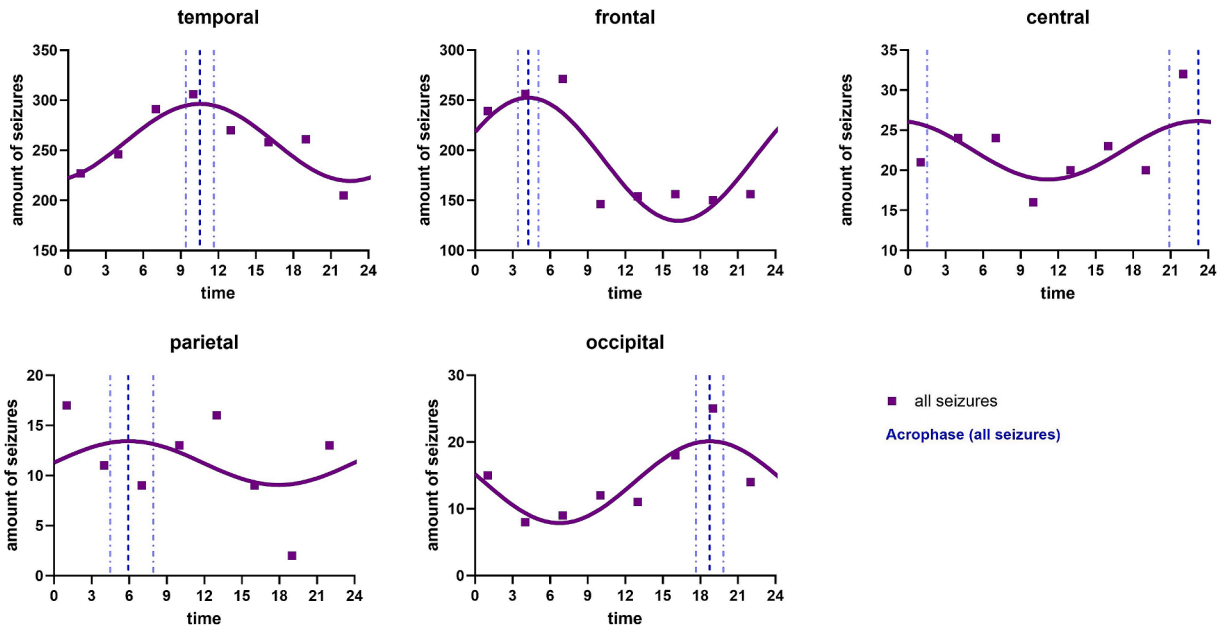

Fig. 1. Cosinor analysis of all seizures divided into groups according to the seizure onset zone. The squares indicate the number of seizures in a 3-hour time bin. The dashed blue lines indicate the acrophase and its 95th confidence level.

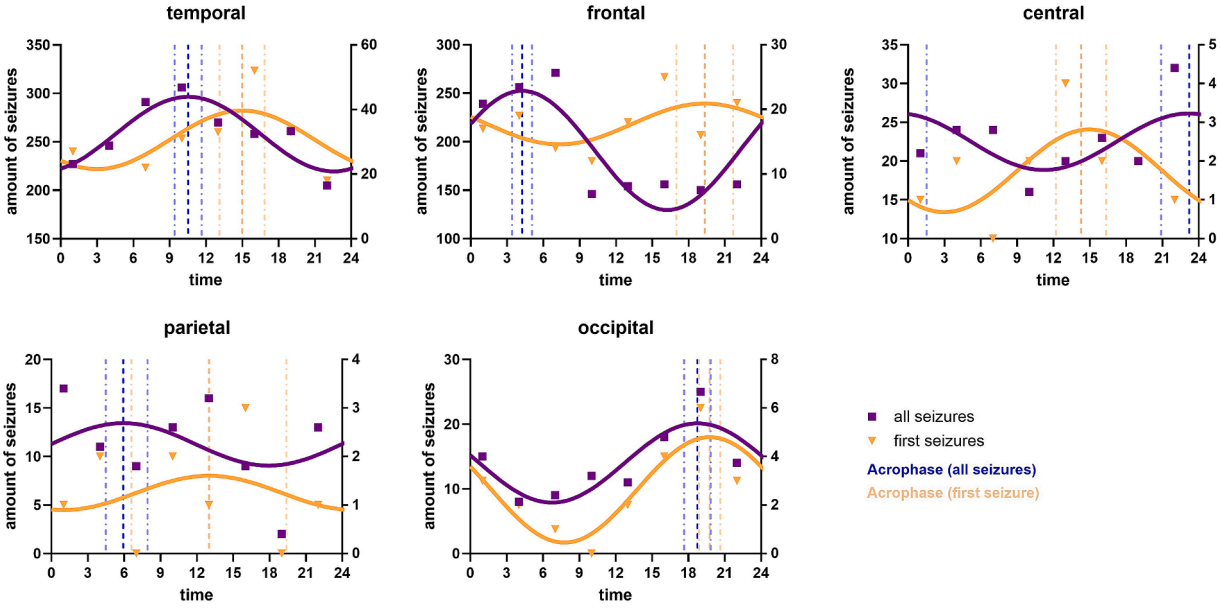

Fig. 2. Cosinor analysis of all seizures (purple curve) and the first seizures (orange curve) grouped by seizure onset zone. Squares represent the number of all seizures in a 3-hour time bin, triangles represent the number of first seizures. The dashed blue lines indicate the acrophase and its 95th confidence level of all seizures, the dashed orange lines indicate the acrophase and its 95th confidence level of the first seizures.

central versus parietal ($p = 0.71$) was did not differ statistically significantly (Supplementary Material Table 2). Since the data didn't fit as well to a cosinor analysis (as it was shown in the zero-amplitude test), these results have to be interpreted with caution.

Comparing the 95th confidence limits of the peak time of the cosinor analysis of the corresponding regions for all seizures versus the first seizure, there was a statistically difference of the peak time of seizures originating from the temporal ($p < 0.01$), frontal ($p < 0.01$), central ($p < 0.01$) and occipital ($p < 0.01$) region (Supplementary Material Table 2).

3.5. *Effect of sleep on seizures arising from different lobes*

Most seizures occurred from the awake state (in total 64.56 %) regardless of the seizure onset zone ($p < 0.01$). Especially seizures arising from the temporal, parietal and occipital lobe (69.77 %, 71.11 % and 70.54 % respectively, $p < 0.01$) tended to occur out of the awake state (Fig. 3). All seizure from sleep came from NREM-sleep. Even seizures from the frontal lobe were more common out of the awake state (56.47 %).

3.6. *Effect of sleep on FBTCS arising from different lobes*

In total, 432 of all seizures were FBTCS (10.94 %). Overall, most

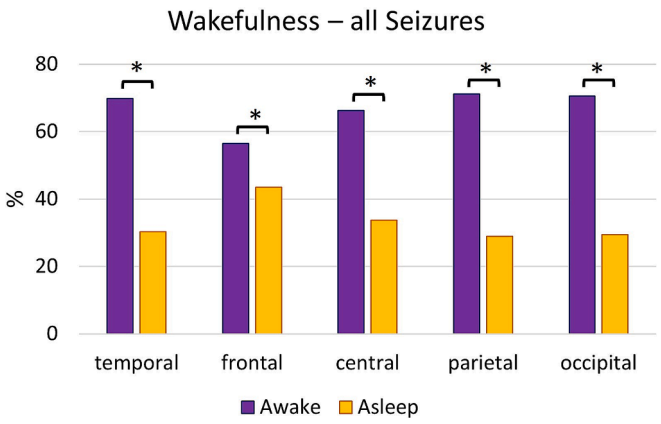

Fig. 3. Percentage of seizures for different seizure onset zones according to the state of wakefulness. * = p–value < 0.05.

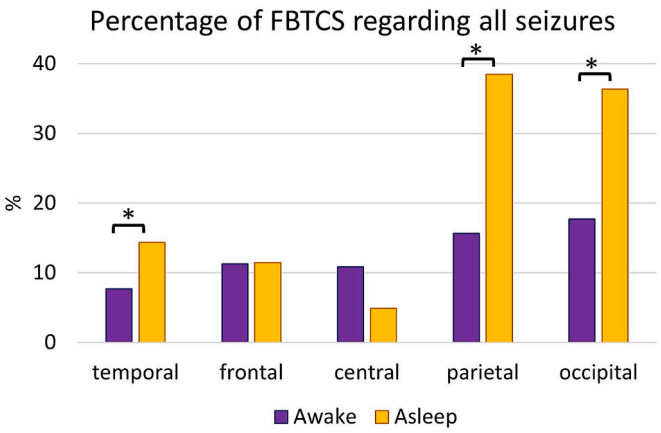

Fig. 5. Percentage of FBTCS in regard to total number of seizures occurring in sleep/awake state. * = p –value < 0.05.

FBTCS occurred out of the awake state (p = 0.009). Regarding the different lobes, only seizures arising from the central lobe showed a significant difference in the occurrence of FBTCS with more FBTCS occurring out of the awake state (p = 0.012) (Fig. 4).

Overall, 11.34 % of frontal, 9.70 % of temporal, 8.84 % of central, 22.22 % of parietal and 23.21 % of occipital seizures progressed to bilateral tonic-clonic seizures.

Comparing the amount of secondary generalization to the number of seizures out of the awake or sleep state, more FBTCS occurred from sleep for parietal (p = 0.018), temporal (p < 0,001) and occipital lobe seizures (p = 0.033). For frontal (p = 0.926) and central region seizures (p = 0.185) no difference could be detected in the amount of secondary generalization of seizures from awake/sleep state (Fig. 5).

4. Discussion

Our data demonstrates that there is a clear rhythmicity of the occurrence of seizures over the 24 h-day, which is most likely a circadianly regulated rhythmicity when considering previous work that has shown circadian timing of seizures [17].

4.1. Rhythmicity of epileptic seizures

The occurrence of seizures is not randomly distributed. Especially for temporal, frontal and occipital lobe seizures a 24 h periodicity could be detected in our study. The periodicity differs depending on the seizure onset zone and taking previous work into account we believe that it is a circadian rhythmicity.

Temporal lobe seizures were reported to occur more likely in the afternoon or with a diurnal distribution [5,15,17]. Here, by analyzing more than 2000 seizures arising from the temporal lobe we identified a peak at 10am in the morning. If only the first seizure is considered, the same afternoon peak was present in our analysis. But with the recording of more seizures, the peak shifted towards earlier in the morning.

Regardless of localization, the peak of onset in the afternoon was seen in all first seizures. Our data suggest that the time of onset of the first seizure may not be representative of the occurrence of subsequent seizures as demonstrated by the analysis of peak time. Thus, to evaluate a periodicity for each patient, more seizures should to be analyzed.

For EVM-purposes, it is standard practice to quickly taper the anti-seizure medication at the beginning of the stay. Therefore, that first seizure in the EVM may represent to the decreasing influence of anti-seizure medications. And since the admission timing and tapering of

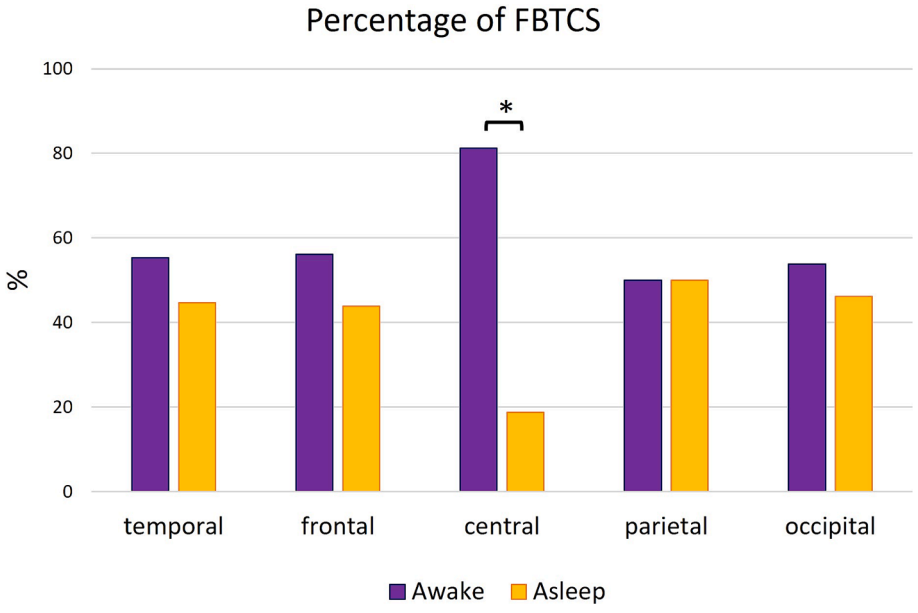

Fig. 4. Percentage of FBTCS for different seizure onset zones according to the state of wakefulness * = p –value < 0.05.

medication follows typically the same pattern, this effect for the first seizure should be interpreted with caution.

Previous studies as mentioned above have typically made the distinction of temporal vs. extratemporal seizure onset only, typically because other regions are not as commonly evaluated for epilepsy surgery and therefore less data is available. Since our study shows a difference in timing for all considered regions, future studies should evaluate not only temporal vs. extratemporal but consider differentiating the other regions.

The occurrence of seizures from the occipital and parietal lobe differs with a 180° circadian phase shift: The probability of occurrence of occipital seizures is highest between 04:00–07:00o'clock in the afternoon and lowest for parietal seizures at the same time [5]. The 24-hour periodicity was not statistically significant for parietal lobe epilepsies in our study, but the trend to an afternoon maximum represents a 180° phase shift compared to occipital lobe epilepsies.

Using data from implanted responsive neurostimulation devices, it could be shown that there is not only a circadian but also multidien, monthly and circannual rhythms in epilepsy [11]. These data have the great benefit of continuous, large-scale data and with that gave new insight of the long-term rhythmicity, but also did so far not include enough extratemporal epilepsies to distinguish between the lobes as discussed above. Furthermore, these data allowed describing rhythms for interictal epilepsy activity, as well [1]. Due to the smaller number of patients studied with implantable devices, it is not yet possible to clearly identify differences in the temporal distribution of seizures for different seizure onset zones.

However, our study showed differences in seizure occurrence probability according to seizure onset zone. For the first time, patients with seizures arising from the central region were included. The evaluation showed a nocturnal maximum for these seizures at around 10 pm. Comparing the acrophase of seizures arising from the central vs. frontal or parietal region, it showed a significant difference. Therefore, we believe that it is important to recognize the central region as a separate seizure origin zone.

4.2. Effect of sleep on seizures arising from different lobes

According to previous research, about half of all seizures arise from the sleep state, especially non-REM-sleep [9,10]. In our study population, by contrast, most seizures occurred from the awake state, regardless of the seizure onset zone.

Seizures arising from the frontal lobe in particular are reported to have an increased occurrence during sleep [4,9].

In our cohort, the maximum of seizures was in the early morning hours (between 4:00 and 6:00 am). However, most patients were awake right before their seizures (56.74 %, $p < 0.01$).

The reason for this discrepancy to former studies could be the smaller number of cases in earlier studies or a reporting bias in studies based purely on patient diaries [12].

4.3. Effect of sleep on FBTCS arising from different lobes

Regarding the secondary generalization of seizures, more FBTCS occurred during wakefulness ($p = 0.009$) when only the total number of seizures is considered. Comparing the number of seizures with secondary generalization to the number of seizures during wakefulness/sleep, in parietal, temporal and occipital lobe sleep promotes secondary generalization. The reason might be a relative hypersynchrony during non-REM sleep which may facilitate spread of partial seizures [2]. Other studies suggest that secondary generalization depends on a thalamocortical network [9].

A better understanding of the circadian rhythm of seizures may help develop chronotypes and chronotherapy. Chronotherapy attempts to determine the optimal medication administration times from a circadian perspective in order to minimize side effects and increase efficiency [7]. Our study shows, though, that the seizure onset zone needs to be considered for this and that possibly sleep is not the only determinant factor, but equally important the circadian distribution.

By knowing the temporal pattern of seizure onset, medications can be targeted and administered at the right time. Multiple studies show promising results in optimizing seizure frequency using chronotherapy. One study reported a benefit in seizure control in 103 patients administering carbamazepine and phenytoin according to chronotypes [18].

5. Limitations

We could not consider the definite pharmacokinetic impact of antiseizure medication tapering on seizure frequency in our study. Antiseizure medication was tapered at the beginning of the recording of all patients, but blood levels of the medication are not done routinely in this situation. The patient's history of seizures and status epilepticus was taken into account so sometimes antiseizure medication was discontinued completely, sometimes it was only reduced.

Antiseizure medication is known to have effects on sleep structure as well and therefore might influence the timing of seizures. Having a large number of seizures to analyze this bias was minimized.

Furthermore, we analyzed up to ten seizures per patient to avoid a bias in overrepresenting patients' results with many seizures. On the other hand, though, patients with few seizures might therefore be underreported.

When evaluating sleep in our patients, the scoring may have been limited by not having EOG and EMG on the patients. Since the temporal leads reflect the eye movements very well and the occipital leads show alpha loss very well, we think that this bias is small, future studies might consider using all necessary polysomnography leads.

6. Conclusion

Seizures originating from the temporal, frontal or occipital lobe follow a 24 h rhythm whereas parietal and central region seizures do not show a 24 h periodicity. Partial seizures tend to occur more during the awake than sleep state, regardless of the seizure onset zone.

The time of the first recorded seizure in Video-EEG-Monitoring may not be representative of subsequent seizures.

Furthermore, seizures originating from the temporal, parietal or occipital lobe exhibit a greater risk to secondarily generalize in sleep compared to the awake state.

By knowing the peaks of seizure occurrence chronotypes can be identified and antiseizure medication can be adjusted accordingly. This might help to enhance seizure control and reduce seizure associated risk (trauma, drowning).

CRediT authorship contribution statement

Katharina Ernst: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Benjamin Erhard:** Data curation, Investigation. **Nicholas Fearns:** Visualization, Conceptualization. **Denise Birk:** Conceptualization, Visualization. **Jan Rémi:** Methodology, Data curation, Conceptualization, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2025.110395.

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