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Diurnal rhythms in seizures detected by intracranial electrocorticographic monitoring: An observational study

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ABSTRACT

Few studies have evaluated human seizure occurrence over the 24-hour day, and only one group has employed intracranial electrocorticography monitoring to record seizures. Circadian patterns in seizures may have important implications in diagnosis and therapy and provide opportunities in research. We have analyzed spontaneous seizures in 33 consecutive patients with long-term intracranial EEG and video monitoring. Several aspects of seizures were noted, including time of day, origin, type, and behavioral state (sleeping/awake). We recorded 450 seizures that showed an uneven distribution over the day, depending on lobe of origin: temporal lobe seizures occurred preferentially between 1100 and 1700 hours, frontal seizures between 2300 and 0500 hours, and parietal seizures between 1700 and 2300 hours. In the awake state, larger proportions of clinical seizures were seen from 0500 to 1100 hours and from 1700 to 2300 hours. During sleep, larger proportions occurred from 1100 to 1700 hours and from 2300 to 0500 hours. Our results suggest that seizures from different brain regions have a strong tendency to occur in different diurnal patterns.

1. Introduction

The unpredictability of epileptic seizures is an important factor in the disabling character of the disease. It has been shown that not all seizures occur randomly [1–5]. Animal studies have provided some answers, as clear diurnal patterns of seizures have been observed in various epilepsy models. For instance, in studies of rodents with limbic epilepsy, it was observed that seizure latency was shorter and more spontaneous seizures occurred during exposure to light than during darkness [6–12].

In humans, patterns of seizure occurrence have been studied, but most authors have assessed only the random or nonrandom character of these patterns [2–4]. Data on precise temporal distribution of seizures, however, are particularly scarce. Four studies have provided details on the temporal distribution of seizures using long-term EEG monitoring, three of these four studies used scalp EEG monitoring [5,8,13]. In one study, the pattern of partial seizure occurrence in adults was compared with that of seizures in an epileptic rat model [8]. It was found that in patients with mesial temporal lobe epilepsy (MTLE), seizures did not occur randomly, but in a sinusoidal daily distribution, comparable to the occurrence of seizures in rats. In another study, clear patterns in both temporal lobe seizures and extra-temporal seizures were demonstrated [13]. In a recent study, we evaluated the temporal distribution of different types of clinical seizures also using scalp EEG. We observed significantly more seizures from 1100 to 1700 hours and significantly fewer seizures from 2300 to 0500 hours [5].

These three studies have provided valuable information; however, they all used scalp EEG monitoring to record seizures. Scalp EEG may not detect all seizures, especially more localized or subtle seizures and seizures arising from deep structures that cannot be detected on the scalp. In addition, muscle artifacts may obscure a fast seizure EEG rhythm. At present, intracranial electrocorticography (ECoG) monitoring (IEM) is the gold standard for recording seizures and delineating epileptic foci without these limitations. To our knowledge, only one recent study used IEM to evaluate the temporal distribution of seizures [14]. These authors found seizures from the parietal, occipital, mesial temporal, and neocortical temporal lobes to be distributed nonuniformly, with peak occurrences at different times over the 24-hour day. In that study, however, only seizures in adults were included and the behavioral state during seizures (sleep or awake) was not addressed.

To understand the pathophysiology of epilepsy, further details on circadian patterns in seizure occurrence need to be ascertained, preferably using IEM for accurate seizure detection. This knowledge may have significant clinical implications for diagnostic procedures and

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timing of therapy in epilepsy. Therefore, we performed a retrospective analysis of all children and adults with various types of seizures who recently underwent long-term intracranial ECoG monitoring in the nationwide epilepsy surgery program in The Netherlands.

2. Methods

2.1. Intracranial ECoG monitoring and video recording systems

Long-term IEM was performed in the Intensive Epilepsy Monitoring Unit at the University Medical Centre in Utrecht. Subdural strips and grids were used for IEM. Strips were eight-electrode arrays made of 5-mm-diameter platinum disks spaced 10 mm between centers. Grids consisted of a multiple of eight 5-mm-diameter platinum disks (maximum of 64) in a rectangular array with 10-mm center-to-center distance (Ad-Tech, Racine, WI, USA). In one patient, placement of subdural strips through burr holes was sufficient. In all other patients, subdural strips and grids were placed after craniotomy. Grids were positioned depending on the suspected foci in the particular patient. Additional scalp EEG electrodes were placed according to the 10–20 or 10–10 system. ECoG was recorded with Telefactor equipment (Philadelphia, PA, USA; SF 512 Hz, 16 bits) from 1998 until 2005 and with Micromed equipment (Treviso, Italy; SF 512–2048 Hz, 16–22 bits) from 2005 onward. Furthermore, simultaneous polygraphy (electromyography, electro-oculography, etc.) and electrocardiography were performed. Respiration was monitored with abdominal piezo respiratory effort sensors. Patients were observed continuously through video monitoring. ECoG and video data were saved and archived after interpretation.

Before IEM, antiepileptic drugs (AEDs) were (partially) tapered, tailored to the individual patient. Other medication remained unchanged. Because of the monitoring equipment, patients had to remain in bed during the entire registration. Patients were allowed to sleep at their normal bedtimes and naps during the day were allowed, although they were sometimes disturbed by tests, physicians' rounds, mealtimes, and visiting hours. Monitoring was performed as long as clinically necessary. When the decision was made to resect the epileptic focus, the intracranial grids and strips were removed in the same procedure.

2.2. Inclusion

ECoG recordings of 33 consecutive patients with spontaneous seizures during IEM performed from 1999 to 2008 were included. A seizure was defined as an electroencephalographic epileptic event lasting at least 5 seconds. On the basis of remarks made by the patients and staff and close analysis of the videos, the seizures were assessed as subclinical or as having a clinical correlate. The latter included those limited to an aura.

A seizure cluster was considered one seizure, with the starting point of the first seizure as the start point. Seizures occurring after provocation, for example, hyperventilation or sleep deprivation, were not included. Patients with more than 15 seizures per time bin (see below) on a given day were excluded, as this could lead to erroneous peaks in seizure occurrence. The ECoG data together with the clinical aspects were decisive in determining the origin of each seizure.

2.3. Data analysis

Entire ECoG recordings were evaluated in Utrecht by well-trained technicians of the Clinical Neurophysiology Department and by board-certified clinical neurophysiologists (F.S.S.L., Dr. C.Y. Ferrier). Recent 1.5- or 3-T MRI, PET, and sometimes ictal SPECT scans were available. These data together with other relevant information were reviewed before IEM by the Dutch National Task Force on Epilepsy Surgery, which includes clinical neurophysiologists, neurosurgeons, and psychologists from all epilepsy centers in The Netherlands. From the IEM data, time of occurrence of seizures was noted. Furthermore, occurrence during sleep or while awake, type of seizure (auras, subclinical or clinical), and lobe of origin of the seizures were determined.

To study the temporal distribution of seizures, the 24-hour day was divided into four 6-hour bins. With the expected nadir of core body temperature (approximately 0500 hours) as starting point, the time bins covered the periods 0500–1100 (I), 1100–1700 (II), 1700–2300 (III) and 2300–0500 (IV) hours. The nonparametric binomial test was used to test whether numbers of seizures in the four time bins were significantly different. Under the assumption that seizures occur randomly, the percentage of the total number of seizures in each of the four bins is expected to be 25%. The binomial test measures differences between the expected percentages (25% per time bin) and the percentages calculated in the study. Significance was set at a P level of 0.05. For statistical analysis, SPSS Version 12.0.1 was used.

3. Results

3.1. Subjects

From 1999 to 2008, the seizures of 33 patients were analyzed. The population consisted of 26 adults (9 women: mean age 29.7 years, range 17–45; mean duration of IEM 4.6 days, range 2–8) and 7 children (4 girls: mean age 11.6 years, range 5–15; mean duration of IEM 4.0 days, range 2–6).

Imaging of the brain with MRI revealed dysplasia in 13 patients, a tumor in 5, mesiotemporal sclerosis (MTS) in 3, and multiple causes (cavernomas and MTS) in one. In another five patients various lesions were found (a cyst in two patients, a postabscess tissue scar, posttraumatic and postsurgical defects); six patients had normal MRI scans. Eight other patients were excluded, because four had more than 15 seizures in one time bin, three had no spontaneous seizures, and one had only daytime registrations.

3.2. Distribution of seizures over the day

A total of 450 spontaneous seizures were available for study. The origin was mesial temporal in 85 seizures (6 patients, 5 adults), neocortical temporal in 72 seizures (8 patients, 7 adults), frontal in 190 seizures (14 patients, 10 adults), parietal in 99 seizures (4 patients, 3 adults), and occipital in four seizures of one adult. Although differences between the temporal distribution of seizures in children and adults were not expected, seizures in adults ($n = 312$) were also analyzed separately so the results could be compared with results of other studies that analyzed seizure occurrence only in adults.

Because of scarce data on seizures of occipital origin, these were excluded from analysis.

In seizures of mesial temporal origin, there was a significant peak in the number of seizures from 1100 to 1700 hours ($P = 0.002$) and fewer seizures than average from 0500 to 1100 hours ($P = 0.005$). A similar peak (1100–1700 hours) was observed for seizures of neocortical temporal origin ($P = 0.07$). Frontal seizures occurred significantly more often during the nighttime (2300–0500 hours, $P = 0.049$). Seizures of parietal origin peaked from 1700 to 2300 hours ($P = 0.008$) and were less prevalent from 1100 to 1700 hours ($P = 0.024$). When seizures of adults were analyzed separately, the results were as follows. The distribution of seizures of mesial temporal origin was similar: more seizures from 1100 to 1700 hours ($P = 0.002$) and fewer from 0500 to 1100 hours

Table 1
Temporal distribution in seizures of various origins in children and adults, $n = 450$.

Origin	Time (bin)			
	0500–1100 h (I)	1100–1700 h (II)	1700–2300 h (III)	2300–0500 h (IV)
Mesial temporal	11[a]	34[a]	20	20
Neocortical temporal	15	24[b]	15	18
Frontal	41	50	41	58[c]
Parietal	27	16[c]	36[a]	20
Occipital	1	3	0	0
Sum	95	127	112	116

[a] $P < 0.01$.
[b] $P = 0.07$.
[c] $P < 0.05$ (binomial test).

($P = 0.001$). Fewer seizures from the frontal lobe were seen from 1700 to 2300 hours ($P = 0.036$); this was also observed for seizures from the parietal lobe (1700–2300 hours, $P < 0.001$).

When seizure occurrence in children was evaluated, only frontal seizures (85 seizures in four children) could be analyzed reliably. It was observed that in these children fewer seizures occurred in the morning (0500–1100 hours) than during the rest of the day ($P = 0.04$).

Table 1 lists the numbers of seizures per time bin, distributed according to origin. Fig. 1A illustrates the distributions of seizures of the four probable origins over time in the total population; Fig. 1B does the same for seizures in adults.

To determine whether time of day influences the clinical expression of seizures, we analyzed the proportions of subclinical and clinical seizures per time bin. There were no significant differences between the proportions of subclinical and clinical seizures over the 24-hour day (χ^2 test, $P = 0.42$).

As could be expected, most of the seizures of all origins while the patient was awake occurred during the day. Likewise, most of the seizures during sleep occurred during the night. On comparison of the clinical severity of seizures per time bin, larger proportions of seizures that occurred in the awake state were seen in the morning (0500–1100 hours) and evening (1700–2300 hours). Among seizures that occurred during sleep, larger proportions occurred during midday (1100–1700 hours) and midnight (2300–0500 hours) (Table 2). The distribution of seizures in the awake state or during sleep over the 24-hour day with respect to origin is illustrated in Fig. 2.

The small numbers of seizures in most groups limited statistical analysis of these data.

4. Discussion

In our patients undergoing IEM, seizures of mesial temporal, neocortical temporal, frontal, and parietal origin occurred in a nonrandom distribution over the 24-hour day. Depending on the lobe of origin, the peak prevalence during the 24-hour day differed.

Temporal distribution of seizures in humans has been studied previously, although knowledge is scarce. In three studies in which seizure diaries were used, seizure occurrence was not specified with respect to clock time. When all three studies are taken together, nonrandom seizure patterns were observed in 53% of the 66 subjects [2–4]. Unfortunately, seizure diaries are not as reliable as EEG monitoring, as nocturnal seizures can be missed, patients can have amnesia for their seizures, and psychogenic seizures can be confused with epileptic seizures.

Only three studies have used scalp EEG. The first study regarded patterns of seizures in 96 adult patients with MTLE, lesional TLE, and extra-temporal lobe epilepsy [8]. Seizures in patients with lesional TLE and extra-temporal lobe epilepsy were found to be distributed randomly; however, seizures in patients with MTLE peaked at 1500 hours. In another study describing 26 patients (90 seizures), the seizures of those with TLE peaked from 1500 to 1900 hours and seizures in patients with extra-temporal lobe epilepsy peaked from 1900 to 2300 hours [13]. In this extra-TLE group, five patients with a posterior (parieto-occipital) focus showed a peak in proportion of seizures between 1900 and 2300 hours. Comparison of these results with those of the adults in our IEM study revealed similarity in the prevalence late in the morning and early afternoon for seizures originating from the mesial temporal lobe; however, the peaks in our study were somewhat earlier. When our results for seizures of frontal, parietal, and occipital origin are combined, an extra-temporal pattern can be determined; this did not result in a significant pattern (see Fig. 3). Our results therefore support those of Quigg et al., rather than those of Pavlova et al., although the latter group's results regarding parieto-occipital seizures do tend to echo our results for seizures of parietal origin.

Recently, we analyzed clinical seizures of 100 adults and 76 children who underwent continuous scalp EEG and video monitoring (mean duration 48.8 hours) [5]. For 808 seizures, time of day, classification, origin, and sleep stage were noted. Significantly

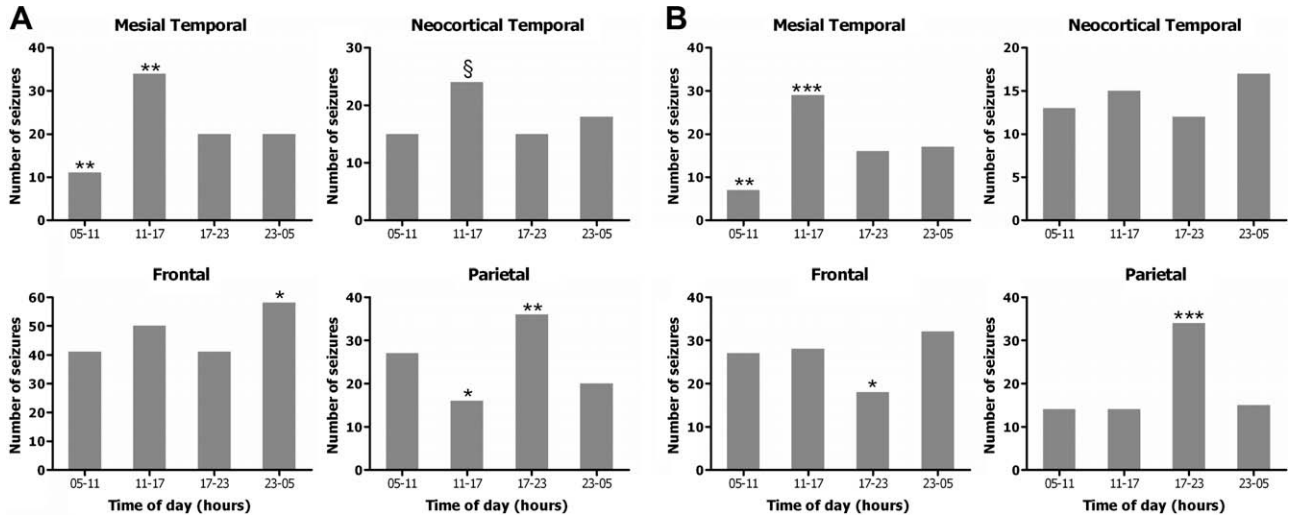

Fig. 1. Bar histogram showing temporal distribution of seizures from different regions of the brain in children and adults (A, $n = 446$) and adults only (B, $n = 308$). Each bar represents number of seizures per 6-hour time bin ($^{*}P < 0.05$, $^{**}P < 0.01$, §$P = 0.07$, $^{***}P < 0.001$).

Table 2
Clinical severity of seizures while awake ($n = 222$) and during sleep ($n = 228$) in children and adults.

	0500–1100 h	1100–1700 h	1700–2300 h	2300–0500 h	All day
While awake	$n = 41$	$n = 94$	$n = 67$	$n = 20$	$n = 222$
Clinical (%)	90.2	64.9	91	75	78.4
Subclinical (%)	7.3	25.5	4.5	20	15.3
Aura (%)	2.4	9.6	4.5	5	6.3
Sum (%)	100	100	100	100	100
During sleep	$n = 54$	$n = 33$	$n = 45$	$n = 96$	$n = 228$
Clinical (%)	68.5	78.8	67	77.1	73.2
Subclinical (%)	31.5	21.2	33	22.9	26.8
Sum (%)	100	100	100	100	100

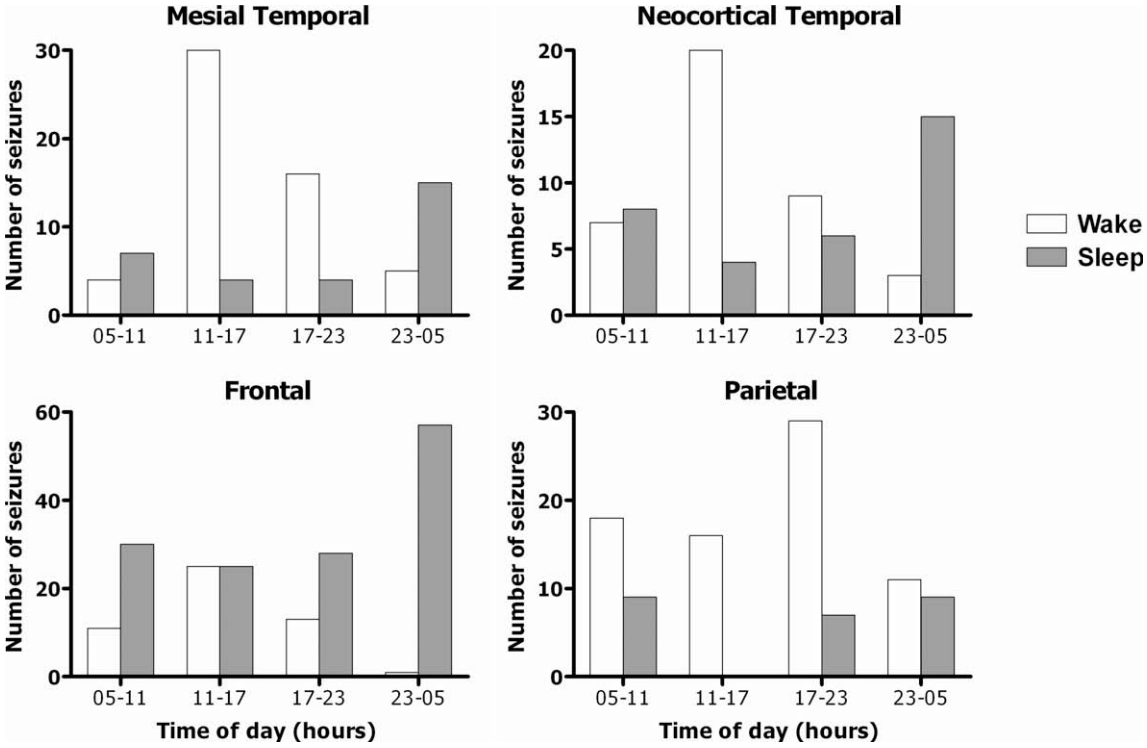

Fig. 2. Bar histogram showing temporal distribution of seizures while awake or during sleep.

more seizures were observed from 1100 to 1700 hours and significantly fewer seizures from 2300 to 0500 hours.

Our current results may be different from the results of these EEG-based studies for several reasons. First, IEM is more accurate in recording seizures, as the seizures are not obscured by muscle artifacts and areas that are not accessible by scalp EEG can be recorded. Also, patient populations differ, as IEM is performed only in presurgical evaluation. These are patients with particularly severe focal epilepsy that is often difficult to localize by noninvasive techniques. Finally, the inclusion criteria in our scalp EEG study differ from those in this study: in our previous study only clinical seizures were included, whereas in this study the definition of a seizure was based mainly on the EEG.

Only one other group has studied the temporal distribution of seizures using IEM. Durazzo et al. analyzed 669 seizures of 131 adult patients [14]. Different nonuniform seizure distributions were observed in seizures of parietal, occipital, frontal, mesial temporal, and neocortical temporal lobe origin. Several similarities can be observed between their results and our results in adults. The afternoon time bins in which seizures of mesial temporal origin peak overlap in the two studies. However, the second peak in Durazzo and colleagues' study (0700–1000 hours) does not correspond to our results, as in our patients significantly fewer seizures were documented. We observed fewer frontal seizures from 1700 to 2300 hours, which corresponds in part to the low (1600–1900 hours) in the study by Durazzo et al. Finally, we observed more parietal seizures from 1700 to 2300 hours. This distribution differs

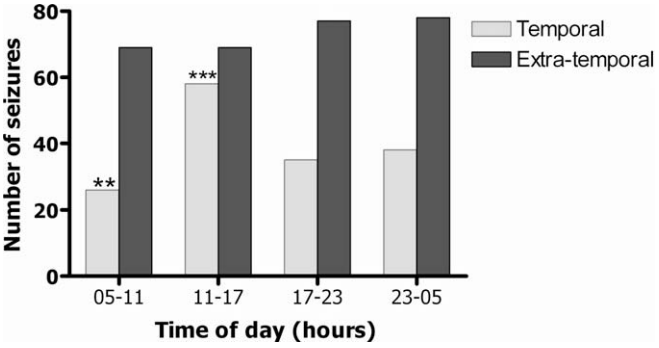

Fig. 3. Bar histogram showing temporal distribution of seizures from the temporal lobe and the extra-temporal lobes ($^{**}P < 0.01$, $^{***}P = 0.001$).

substantially from the Gaussian-like distribution with a low in the afternoon and early evening found by Durazzo et al., though our results are similar to those in patients with a parieto-occipital focus in the scalp EEG study of Pavlova et al., as noted above [13].

With respect to the methodology of these two studies, a few differences can be noted. First, Durazzo et al. were able to include more patients and seizures, but they used eight randomly chosen seizures per patient, while we included all spontaneous seizures of our patients, handling strict exclusion criteria. Also, they chose to use 3-hour time blocks instead of our 6-hour time bins. These distinctions may explain the differences in results.

Several strengths of our study can be mentioned. First, the gold standard IEM was used to record seizures. All ECoG recordings were reviewed at least twice and all subjects were discussed at length by the Dutch National Task Force on Epilepsy Surgery, which determined the epileptic focus precisely on the basis of a concordance of IEM, imaging, patient's history, and clinical observations. Also, our IEM study is the first to include children as well as adults. Furthermore, we are the first to review seizures with IEM during both the awake state and sleep. Seizures from all parts of the brain (apart from the occipital lobe) were taken into account and analyzed separately. Finally, by excluding patients with more than 15 seizures per time bin, counting a seizure cluster as one seizure, and excluding provoked seizures, we prevented erroneous peaks in seizure occurrence.

A number of limitations remain. First, our database of patients undergoing IEM does not represent the average population of patients with epilepsy. Second, the extent of influence of endogenous and exogenous factors on seizures and seizure timing is not known. Daily activities such as mealtimes and physical exercise may influence timing of seizures. Also, the effects of AEDs on the distribution of seizures remain to be elucidated, as reports disagree [1,15]. Further, anesthetics may affect seizure frequency, having pro- or anticonvulsant effects [16]. In our study only 4 of 450 seizures occurred on the same day as the operation. Therefore, anesthesia probably has no proconvulsive effect relevant to the results of our study.

To sort out the precise effects of exogenous and endogenous factors on epilepsy and seizure distribution, subjects would have to be studied under constant conditions [17]. Also, animal studies could provide answers to these questions. This will be the subject of further study.

In the current study, we have taken wakefulness and sleep into account. However, during IEM the normal sleep–wake cycles are difficult to maintain, as the process of implantation and monitoring is fatiguing for patients. Furthermore, as patients remain in bed during IEM, sleep is easily initiated at abnormal times for particular patients. The precise influence of the natural sleep–wake cycle is therefore difficult to interpret in this study.

The exact basis of diurnal patterns in seizure occurrence remains to be elucidated. The circadian rhythm, with the master circadian pacemaker located in the suprachiasmatic nuclei, may play an important role in these seizure patterns. This pacemaker generates and maintains circadian rhythms in many physiological and psychological processes, including sleep–wake cycle, core body temperature, blood pressure, and secretion of several hormones [18]. It is conceivable that some of these body functions are important to the rhythm in seizure occurrence or even that this pacemaker itself generates a rhythm in seizures. These ideas will be subject of a large prospective study in our epilepsy and sleep center.

As a whole, our study clearly suggests that seizures do not occur randomly, but seem to take place in daily patterns. Different temporal patterns can be recognized in patterns of seizures from different parts of the brain. Recognition of patterns in seizure occurrence is an important first step in taking the rhythmicity of seizures into account in the diagnosis and treatment of epilepsy. However, more research is needed to further explore these daily patterns and to identify underlying mechanisms that lead to these diurnal rhythms of seizures.

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