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# Predicting diurnal and sleep/wake seizure patterns in paediatric patients of different ages

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**ABSTRACT** – *Aim*. To identify factors that influence diurnal and sleep/wake seizure timing in children undergoing tapered drug withdrawal in an epilepsy monitoring unit. *Methods*. Medical charts of patients that underwent video-EEG were reviewed. Seizures were evaluated based on their occurrence in three-hour time intervals (bins) and between wakefulness and sleep. Patients were classified according to EEG localisation and age: infants (≤3 years), children (3-12 years), and adolescents (>12-21 years). Analysis utilising generalised estimating equations with a negative binomial distribution was performed. *Results*. A total of 390 patients (188 girls; mean age: 9.2 years; SD: 6.0) had 1,754 seizures. Generalised seizures (109 patients; 490 seizures) occurred more during wakefulness ($p<0.001$) and during the day ($p<0.001$). Modelling revealed a greater occurrence of seizures at night with increasing age ($p=0.046$). Temporal lobe seizures (62 patients; 271 seizures) occurred overall more frequently during wakefulness ($p=0.03$). Frontal lobe seizures (41 patients; 184 seizures) occurred more frequently during wakefulness in infants ($p<0.05$) and more frequently during sleep in adolescents ($p<0.0001$). Adolescents with frontal lobe seizures were 3.6 times more likely to have seizures during sleep compared to other children (95% CI: 1.8-7.2). *Conclusion*. These findings are suggestive of changes in circadian rhythmicity that may alter seizure susceptibility in different age groups. The results may assist in prediction of periods of greatest seizure propensity.

**Key words:** long-term monitoring, video-EEG, semiology, circadian pattern, diurnal pattern, seizure prediction

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Seizures frequently do not occur randomly (Janz, 1962; Quigg *et al*., 1998; Durazzo *et al*., 2008; Loddenkemper *et al*., 2011a; Zarowski *et al*., 2011; Pavlova *et al*., 2012;). The reasons for these non-random seizure patterns are not completely known. EEG localisation has been shown to correlate with seizure timing (Zarowski *et al*., 2011). Specifically, generalised and temporal lobe seizures have been noted to occur more frequently during wakefulness, and frontal lobe seizures occur more frequently during sleep (Loddenkemper *et al*., 2011a).

Other studies have suggested an effect of age on seizure timing with respect to specific seizure semiology (Ramgopal *et al*., 2012a; Ramgopal *et al*., 2012b). Additional information with which to predict propensity to seize at certain times is not available. The use of multiple individualised variables may allow for improved seizure prediction. The availability of novel seizure tracking methods, including video-EEG recordings, automatic seizure detection systems, and ambulatory electronic seizure diaries, may provide additional feasibility of such systems in the future (Loddenkemper, 2012; Poh *et al*., 2012).

Previous studies have established circadian patterns in patients using limited datasets. In this study, we aimed to identify individual clinical factors that influence the timing of seizures. This analysis was performed using an expanded dataset, previously used to identify broad day/night and sleep/wake patterns in seizures, to investigate seizure prediction models. Such information would be of clinical use in formulating seizure prediction models and treatment at times of greatest susceptibility to seizures (Yegnanarayan *et al*., 2006; Loddenkemper *et al*., 2011b; Guilhoto *et al*., 2011).

## Methods

### Patient population

The patient population analysed in this study also included a dataset, a small part of which has been previously reported (Loddenkemper *et al*., 2011a; Zarowski *et al*., 2011; Ramgopal *et al*., 2012a; Ramgopal *et al*., 2012b; Sanchez Fernandez *et al*., 2013). We retrospectively reviewed video-EEG monitoring data and clinical information of consecutive paediatric patients undergoing long-term monitoring (LTM) over a five-year period. Prior to data acquisition, institutional review board approval was obtained for this study. Paediatric patients $\leq$21 years with recorded epileptic seizures were included. Antiepileptic medications were tapered individually for each patient. Patients were kept on their individual sleep/wake schedules for the duration of the inpatient stay as much as possible. Patients with paroxysmal events and invasive monitoring were not included. Prior to study initiation, ethics approval was obtained by the Boston Children's Hospital Institutional Review Board.

### EEG monitoring

Only seizures with clinical manifestations and an EEG correlate were considered. Patients underwent EEG monitoring utilising the 10-20 international system of electrode placement and placement of additional anterior temporal leads. EEG monitoring was carried out in a specialised unit with closed-circuit television, monitored by dedicated EEG technicians. All material with relevant clinical information was archived. When the time of seizure onset was discordant between clinical and EEG features, the time according to EEG was given precedence.

### Semiological and EEG Analysis

All seizures were classified according to the 2001 International League Against Epilepsy seizure classification criteria, considering only the first phase of seizure semiology (Blume *et al*., 2001). Two independent board-certified clinical neurophysiologists carried out video-EEG analysis. Discrepancies in diagnosis, occurring in $<$5% of cases, were settled by a third reviewer, whose decision was considered final. Seizure localisation was ascertained by scalp EEG recordings. In patients in whom multiple regions of ictal EEG onset were found or in whom there was a discrepancy between ictal and interictal findings, seizures were classified under a multilobar category. To facilitate statistical analysis, we classified individual semiology into larger groups. Motor seizures included seizures with clonic, tonic, tonic-clonic, automotor, hypermotor, myoclonic, versive, gelastic, and complex motor semiology. Auras included somatosensory, auditory, olfactory, abdominal, and psychic auras. The atonic/hypomotor group included atonic, astatic, and hypomotor seizures. Dyscognitive seizures and epileptic spasms were classified into separate groups.

### Diurnal and sleep/wake analysis

Seizures were classified according to EEG localisation, as determined by EEG monitoring. The timing of seizures in relation to 3-hour time intervals (bins) over a 24-hour cycle was classified. Seizures were also classified based on their occurrence in two 12-hour bins: day (6 a.m.-6 p.m.) and night (6 a.m.-6 p.m.). In addition, the occurrence of seizures, according to their timing during wakefulness or sleep, was recorded. Sleep/wake status prior to seizure was determined using both EEG and video.

### Age groups

Diurnal and sleep/wake patterns of seizures were classified according to patient age. Three patient age groups were used: (1) infants, defined for the purpose of this study, of less than or equal to 3 years of age (≤3 years); (2) children, greater than 3 but less or equal to 12 years of age (3-12 years); and (3) adolescents, greater than or equal to 12 years of age (>12-21 years).

### Data analysis

To investigate differences in seizure peaks between wakefulness/sleep, day/night, or 3-hour time blocks, a binomial test was conducted, relative to localisation, for each age group. Formal analysis was then undertaken using a generalised linear model with a negative binomial distribution to account for multiple seizures per subject. This model formally tested whether differences in average seizures during wakefulness (*vs*. sleep) or daytime (*vs*. night-time) varied, based on age, according to EEG localisation. If there was a significant difference in age variation ($p<0.05$), we then explored if the impact of potential confounders changed these results. Gender, presence/absence of MRI lesion, semiology subtype, and medications were tested as potential confounders.
In addition, all subjects were used for an analysis to explore whether possible factors, such as age, gender, EEG localisation, number of medications, and MRI abnormality, were useful to predict seizure occurrence out of wakefulness or sleep, while adjusting for seizure semiology. A generalised estimating equation with a binomial distribution was used. *P* values less than 0.05 were considered significant.

## Results

### Patient population

Of the 955 patients, 390 (188 girls; mean age: 9.2; standard deviation: 6.0 years) met the inclusion criteria (*figure 1*). A total of 1,754 seizures were recorded in this group. Of these, 109 patients had 490 generalised seizures, 62 patients had 271 temporal lobe seizures, 41 patients had 184 frontal lobe seizures, 11 patients had 50 parietal lobe seizures, 2 patients had 13 occipital lobe seizures, and 165 patients had 746 multilobar seizures. Descriptive data on this population is provided in *tables 1 and 2*.

### Diurnal and day/night patterns based on EEG localisation

Overall, generalised seizures occurred most frequently at 6-9 *a.m*. ($p<0.001$), 9 *a.m*.-12 *p.m*. ($p<0.05$), 12 *a.m*.-3 *p.m*. ($p<0.01$), and 3-9 *a.m*. ($p<0.05$) out of wakefulness. Temporal lobe seizures were most frequent at 9 *a.m*.-12 *p.m*. ($p<0.05$) and 12 *p.m*.-6 *p.m*. ($p<0.01$) out of wakefulness and at 3-6 *a.m*. out of sleep ($p<0.05$). Frontal lobe seizures occurred most frequently at 12-3 *a.m*. ($p<0.001$) and 3-6 *a.m*. ($p<0.05$) out of sleep. Parietal lobe seizures were most common at 3-6 *a.m*. during sleep ($p<0.01$). Multilobar seizures were most common at 9-12 *a.m*. ($p<0.001$), 3-6 *p.m*. ($p<0.01$), and 6-9 *p.m*. ($p<0.001$) during wakefulness and at 12-3 *a.m*. ($p<0.0001$), 3-6 *a.m*. ($p<0.001$), and 6-9 *a.m*. ($p<0.01$) during sleep. Frontal lobe seizures occurred more frequently at night ($p<0.05$), and temporal ($p<0.05$) and generalised ($p<0.0001$) seizures occurred more frequently during the day.

### Seizure occurrence based on sleep/wake state

Frontal lobe seizures occurred more frequently during sleep ($p<0.001$) whereas generalised and temporal lobe seizures occurred more frequently during wakefulness ($p<0.0001$). All recorded occipital lobe seizures occurred out of wakefulness, but numbers were small in this subgroup. Parietal and multilobar seizures showed no distinct sleep/wake pattern.

### Semiological analysis

Using the semiological subgroups, we identified specific patterns for seizures according to localisation. For seizures arising from the frontal lobe, motor seizures occurred more frequently during sleep ($p<0.0001$) and atonic/hypomotor seizures occurred more frequently out of wakefulness ($p<0.05$). For temporal lobe seizures, auras ($p<0.0001$) and dyscognitive seizures ($p<0.01$) occurred more frequently during wakefulness. For multilobar seizures, auras ($p<0.0001$) and atonic/hypomotor seizures ($p<0.001$) occurred more frequently during wakefulness, and motor seizures occurred more frequently during sleep ($p<0.05$).

### Age analysis

We performed subgroup analyses for age with generalised, temporal, frontal, and multilobar seizures using binomial test results and modelling. Due to small numbers, age analysis was not feasible for occipital and parietal lobe seizures.

### Binomial results

*Generalised seizures*
Infants were more likely to have seizures between 6 *a.m*. and 3 *p.m*. ($p<0.05$), whereas children had more seizures between 6-9 *a.m* and 12-3 *p.m*. ($p<0.05$). Adolescents had more seizures at 6-9 *a.m* ($p<0.05$) and

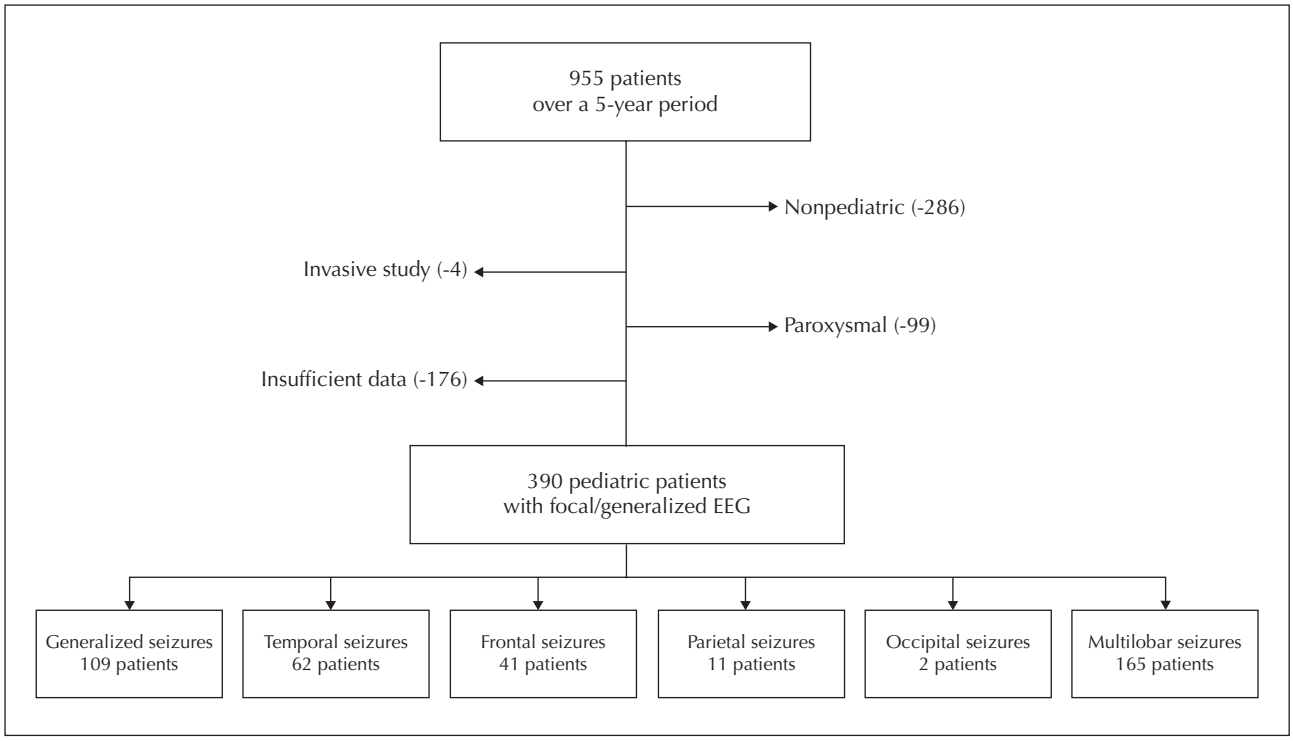


**Figure 1.** Patient selection.

at 6-9 *p.m*. ($p<0.05$). Patients with generalised seizures were more likely to have seizures during wakefulness in all three tested age groups ($p<0.01$). Infants and children were also more likely to have seizures during the day ($p<0.0001$), but this was not the case for adolescents.

*Temporal lobe seizures*

Infants with temporal lobe seizures had a diurnal seizure peak at 3-6 *a.m* ($p<0.05$). Children did not have a diurnal peak but were noted to have more seizures out of wakefulness ($p<0.05$). Adolescents ($\geq$12 years) had more seizures at 12-3 *p.m* ($p<0.01$), out of wakefulness ($p<0.01$), and during the day ($p<0.05$).

*Frontal lobe seizures*

Infants with frontal lobe seizures had more seizures out of wakefulness ($p<0.05$). Children had more seizures at 9 *p.m*-12 *a.m* ($p<0.01$), 12 *a.m*-3 *a.m* ($p<0.05$) and at night ($p<0.0001$). Adolescents had more seizures between 6 *a.m* and 12 *p.m* ($p<0.05$) and out of sleep ($p<0.0001$).

*Multilobar seizures*

Infants had more seizures at 9 *a.m*-12 *p.m* ($p<0.05$), 3-6 *p.m* ($p<0.01$), during the day ($p<0.0001$), and during wakefulness ($p<0.0001$). Children had more seizures at 12-3 *a.m* ($p<0.05$) and 6-9 *a.m* ($p<0.01$) and adolescents had more seizures at 6-9 *a.m* ($p<0.05$). No sleep/wake or day/night seizure patterns were found in children and adolescents with multilobar epilepsy.

## Modelling

*Generalised seizures*

There was an overall predisposition toward having more seizures during the day ($p<0.001$). There was also moderate evidence to suggest an increased likelihood of generalised seizures occurring at night with increasing age ($p=0.046$; *figure 2*). This relationship was not impacted when any potential confounders were added to the model ($p<0.05$).

*Temporal seizures*

The average number seizures was significantly higher when subjects were awake. The odds ratio of temporal lobe seizures out of wakefulness was 2.7 (95% CI: 2.2-3.3). The odds ratio of seizures out of sleep was comparatively lower (OR: 1.6; 95% CI: 1.2-2.3). There was no evidence to suggest the occurrence of day/night or sleep/wake seizure pattern based on patient age.

*Frontal seizures*

There was an overall trend towards seizure occurrence out of sleep ($p=0.07$). As age increased, subjects

**Table 1.** Descriptive data of patient population

| **Total patients (seizures) 390 (1,754)** | | |
|---|---|---|
| Number of girls | 188 | |
| Mean age (SD; range) | 9.22 (6.0; 0.08-21) | |
| Mean V-EEG duration (SD; range) | 4.99 (2.3; 1-16) | |
| **Seizure localisation** | ***patients*** | ***seizures*** |
| Generalised | 109 | 490 |
| Frontal | 41 | 184 |
| Temporal | 62 | 271 |
| Parietal | 11 | 50 |
| Occipital | 2 | 13 |
| Multilobar | 165 | 746 |
| **MRI findings** | ***patients*** | ***seizures*** |
| Normal | 166 | 777 |
| Lesional | 193 | 860 |
| No MRI | 31 | 117 |
| **MRI site of lesion** | ***patients*** | ***seizures*** |
| Frontal | 21 | 90 |
| Mesial temporal | 32 | 158 |
| Neocortical temporal | 1 | 5 |
| Parieto-occipital | 16 | 68 |
| Perirolandic | 2 | 6 |
| Temporo-occipital | 11 | 35 |
| Temporal | 12 | 56 |
| Parietal | 2 | 8 |
| Occipital | 2 | 12 |
| Mesial frontal | 1 | 3 |
| Other lesion | 93 | 419 |
| **MRI side of lesion** | ***patients*** | ***seizures*** |
| Left | 67 | 303 |
| Right | 61 | 272 |
| Bilateral | 37 | 151 |
| Diffuse | 28 | 134 |
| **MRI type of lesion** | ***patients*** | ***seizures*** |
| Cortical dysplasia | 33 | 143 |
| Hippocampal sclerosis | 23 | 93 |
| Tumour | 13 | 56 |
| AV malformation | 1 | 7 |
| Encephalomalacia | 6 | 5 |
| Gliosis | 1 | 4 |
| Volume loss, unspecified | 11 | 43 |
| Cystic lesion | 1 | 3 |
| Status post resect | 3 | 20 |
| Tuberous sclerosis | 12 | 42 |
| Rasmussen | 1 | 19 |
| Sturge-Weber | 14 | 9 |
| Other lesion | 74 | 416 |
| **Antiepileptic Drugs** | ***patients*** | ***seizures*** |
| None | 59 | 258 |
| One | 91 | 353 |
| Two | 118 | 521 |
| Three | 18 | 433 |
| Four or more | 19 | 93 |
| Unspecified | 85 | 96 |

were more likely to have a seizure while asleep ($p$=0.02). This trend was not impacted when any potential confounders were added to the model. There was no significant night *vs*. day occurrence for seizures ($p$=0.2). Although no differences in day/night seizure occurrence were noted, the average number of seizures in each age category suggested that infants were more likely to have a seizure during the day compared with the other two age groups (*figure 2*).

*Multilobar seizures*

Overall, there was no significant difference in the occurrence of seizures during sleep/wakefulness or night/day. Although these trends did not differ based on age of the child, the estimates of the average number of seizures by age group suggest that infants were more likely to have a seizure during wakefulness and daytime.

**Prediction modelling**

Modelling revealed that both age and EEG localisation were significant factors in predicting the occurrence of seizures in sleep and wakefulness (*table 3*). The estimated adjusted odds ratio for age was 0.9592. For a one-year increase in age, the adjusted odds ratio of having a seizure out of wakefulness decreased by a factor of 0.9592 (95% CI: 0.9254-0.9441; $p$=0.023) while controlling for localisation and seizure semiology. The model thus suggested that subjects are less likely to have a seizure out of wakefulness with increasing age. In addition, EEG localisation (generalised or focal) was also found to be a significant factor in predicting when the seizure will occur; the adjusted odds ratio of 1.9527 (95% CI: 1.1869-3.2374; $p$=0.008) indicated that subjects were more likely to have a seizure out of wakefulness in the setting of generalised seizures.

**Table 2.** Patient population according to EEG localisation.

| | **Generalised seizures** | | **Temporal** | | **Frontal** | | **Parietal** | | **Occipital** | | **Multilobar** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients | 109 | | 62 | | 41 | | 11 | | 2 | | 165 | |
| Number of seizures | 490 | | 271 | | 184 | | 50 | | 13 | | 746 | |
| Number of girls | 50 | | 31 | | 22 | | 5 | | 0 | | 80 | |
| Median seizures/subject | 4 | | 4 | | 5 | | 3 | | 7.5 | | 4 | |
| Mean age±SD (median, range) | 6.8±5.7 years (5 years, 2 months-20 years) | | 12.6±5.7 years (13.5 years, 5 months-21 years) | | 10.7±5.4 years (10 years, 1 month-20 years) | | 9.1±4.1 years (10 years, 2 months-15 years) | | 12 years (4-20 years) | | 9.14±5.9 years (9 years, 3 months-21 years) | |
| **Semiology** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** |
| Aura | 2 | 8 | 27 | 127 | 9 | 39 | 4 | 24 | 1 | 5 | 27 | 109 |
| Motor | 61 | 281 | 28 | 123 | 28 | 128 | 6 | 25 | 1 | 8 | 111 | 528 |
| Loss of consciousness | 18 | 81 | 5 | 19 | 3 | 1 | 1 | 1 | 0 | 0 | 7 | 31 |
| Atonic/hypomotor | 14 | 62 | 2 | 2 | 1 | 16 | 0 | 0 | 0 | 0 | 16 | 62 |
| Epileptic spasms | 14 | 58 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 16 |
| **MRI findings** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** |
| Normal | 71 | 307 | 16 | 68 | 16 | 88 | 7 | 31 | 0 | 0 | 56 | 283 |
| Lesional | 26 | 135 | 43 | 194 | 21 | 89 | 4 | 19 | 2 | 13 | 97 | 410 |
| No MRI | 12 | 48 | 3 | 9 | 4 | 7 | 0 | 0 | 0 | 0 | 12 | 53 |
| **Age groups** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** | ***patients*** | ***seizures*** |
| ≤3 | 42 | 170 | 6 | 13 | 3 | 15 | 1 | 3 | 0 | 0 | 38 | 186 |
| 3-12 | 40 | 208 | 19 | 104 | 21 | 101 | 9 | 43 | 1 | 8 | 63 | 314 |
| >12 | 27 | 112 | 37 | 154 | 17 | 68 | 1 | 4 | 1 | 5 | 64 | 246 |

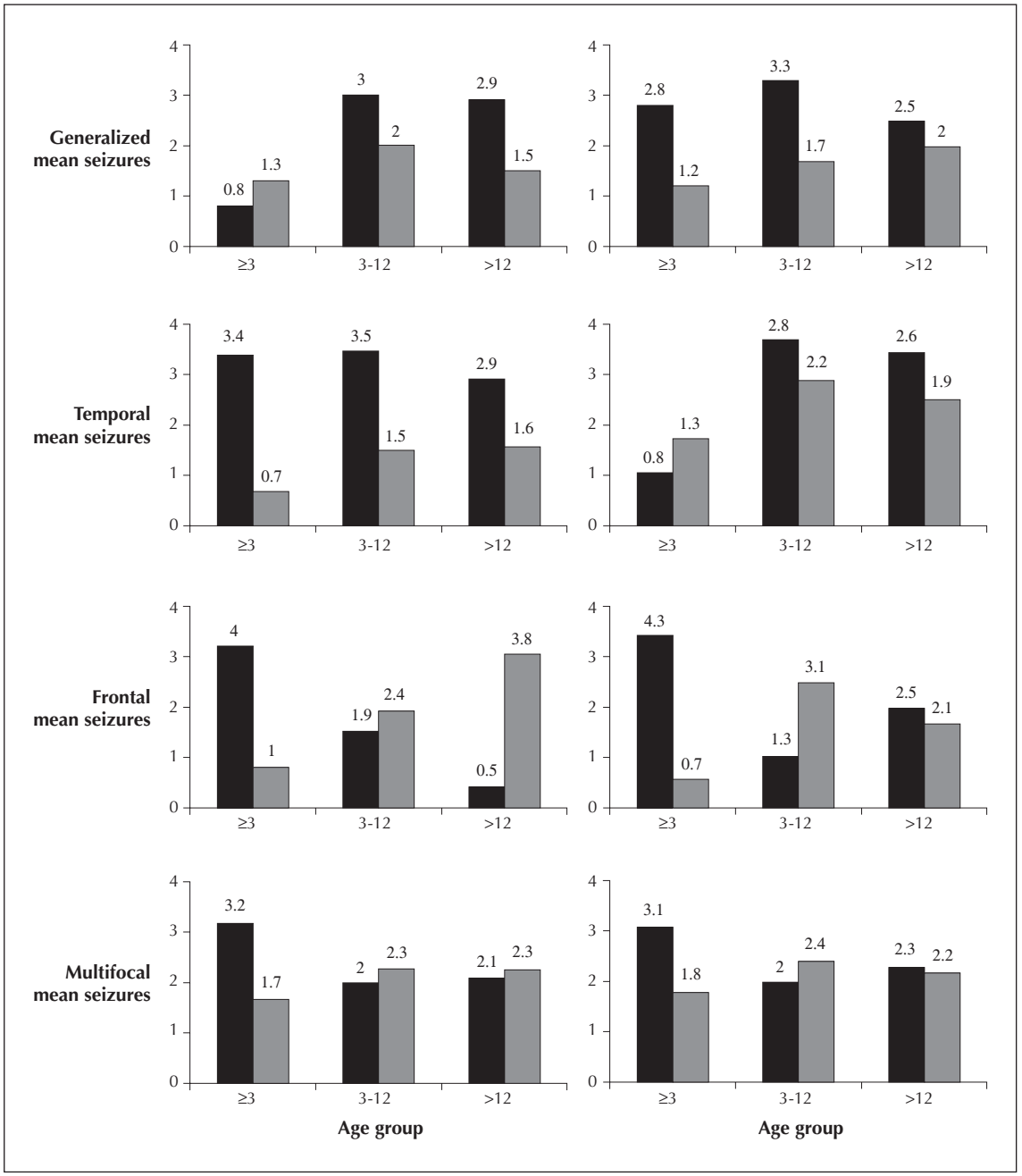


**Figure 2.** Mean number of generalised, temporal, frontal, and multifocal seizures out of wakefulness *vs*. sleep and during the day *vs*. night, following generalised linear mixed model analysis. Patients with frontal seizures had more seizures during sleep with increasing age ($p$=0.02) and patients with generalised seizures had more seizures at night with increasing age ($p$=0.046).

**Table 3.** Adjusted odds of a seizure occurrence out of wakefulness while controlling for seizure types.

| Variable | Estimate (SE) | Adjusted odds (95% CI) | *p* value |
|---|---|---|---|
| Age (years) | -0.042 (0.0183) | 0.96 (0.93, 0.99) | 0.023 |
| Localisation (generalised *vs*. focal) | 0.674 (0.2566) | 1.95 (1.19, 3.24) | 0.008 |

**Table 4.** Intercept estimates used to calculate the log odds of seizure out of wakefulness for each seizure type when adjusting for age, localisation, and seizure semiology.

| Seizure type | Intercept |
|---|---|
| Somatosensory aura | 1.72 |
| Abdominal aura | 0.85 |
| Clonic | 0.16 |
| Tonic | -0.079 |
| Tonic-clonic | -0.42 |
| Automotor | 0.28 |
| Hypermotor | -0.17 |
| Dyscognitive | 1.13 |
| Atonic | 1.70 |
| Hypermotor | 1.54 |
| Myoclonic | 1.20 |
| Versive | 0.16 |
| Epileptic spasm | 0.51 |

The log of odds for the risk of a seizure occurring out of wakefulness can be calculated using the following formula:
Log of odds (seizure risk out of wakefulness) = intercept – 0.042 * age + 0.67 * (generalised).

Using the data from prediction modelling, we created an equation to calculate the seizure likelihood out of wakefulness, as a function of localisation (generalised *vs*. focal), seizure semiology, and patient age:

$$\text{Log of odds}\left(\text{seizure risk out of wakefulness}\right) = \text{intercept} - 0.042{*}\text{age} + 0.67{*}\left(\text{generalised}\right)$$

The intercept variables can be found in *table 4*. The generalised variable should be 1 if the seizure is generalised and 0 if non-generalised. An inverse of the odds can be taken to determine the probability of a seizure occurring out of wakefulness.

## Discussion

Our data demonstrate that seizures occur in diurnal and sleep/wake patterns that vary depending on ictal seizure localisation. In addition, we found that some of these patterns varied according to patient age. Using the data from prediction modelling, we were able to create a model to provide the likelihood of a seizure occurring out of wakefulness as a function of patient age, seizure semiology, and localisation.

### Patterns of focal and generalised seizures

Seizure localisation is an important aspect in predicting seizure occurrence out of sleep and wakefulness. In our dataset, likely, in part, due to high numbers in these groups, this appears to be particularly relevant for generalised, frontal, and temporal seizures.

### Generalised seizures

Generalised seizures occur more frequently out of wakefulness and particularly in the morning. A study comparing 144 patients with seizures predominantly occurring out of sleep to 976 patients with seizures predominantly occurring out of wakefulness found that patients with idiopathic generalised seizures had ictal events more frequently out of wakefulness (Goel *et al*., 2008). These findings are also consistent with previous results from related analyses in smaller patient series (Loddenkemper *et al*., 2011a; Zarowski *et al*., 2011). Generalised myoclonic seizures in patients with juvenile myoclonic epilepsy are similarly known to occur most frequently soon after waking (Janz, 1962). Patients with generalised epilepsy have been noted to have an increased propensity to exhibit generalised interictal epileptiform discharges upon awakening (Fittipaldi *et al*., 2001). Our findings may relate to an increase in cortical excitability in generalised epilepsies during early morning hours, demonstrated in one study by transcranial magnetic stimulation (Badawy *et al*., 2009).

### Temporal lobe epilepsy

Temporal lobe seizures have been documented to occur more frequently out of wakefulness. Our results provide additional information to preliminary analyses from a smaller related patient series (Loddenkemper *et al*., 2011a; Kaleyias *et al*., 2011) and are now the basis for a prediction model that may be used in clinical practice. A study analysing the occurrence of focal epilepsies in 133 adults and children found that both mesial temporal and neocortical temporal seizures were more likely to occur during wakefulness (Herman *et al*., 2001). Temporal lobe seizures were found to occur out of wakefulness more frequently compared to extratemporal lobe seizures in a retrospective study with 90 adults (Pavlova *et al*., 2004). In a study based on retrospective analysis of 94 patients with either mesial temporal or neocortical temporal lobe seizures, a bimodal distribution was noted in these events, with many seizures occurring either in the evening or early morning (Durazzo *et al*., 2008).

### Frontal lobe epilepsy

In contrast to temporal lobe seizures, frontal seizures occur often out of sleep. Based on a series of 16 patients who underwent surgical management for frontal lobe epilepsy, it was reported that 50% of these patients had exclusively nocturnal seizures (Laskowitz *et al*., 1995). Similarly, based on a retrospective study including 20 patients with frontal lobe epilepsy, a trend for these seizures to occur during sleep was identified

(Herman *et al.*, 2001). Findings also corroborate previous results by the authors using more limited datasets (Loddenkemper *et al.*, 2011a; Kaleyias *et al.*, 2011). An outpatient study performed using a digital EEG recording system found the peak in frontal lobe seizures to range between 5:15 and 7:30 *a.m.*, further supporting our results (Pavlova *et al.*, 2012).

### Occipital and parietal lobe seizures

All of the occipital lobe seizures occurred during wakefulness, but numbers were small. One study identified a diurnal peak in occipital lobe seizures between 4 and 7 *p.m.* (Durazzo *et al.*, 2008). Data on parietal seizures in the published literature are limited.

### Relationship between age and seizure onset

Though a variety of studies have evaluated circadian, sleep/wake and day/night seizure patterns, an analysis of the age effect on these patterns has not been performed. Age-related changes in circadian patterns have been well characterised (Watamura *et al.*, 2003; Randler, 2011; Crowley *et al.*, 2012;).

### EEG changes

Electrical activity of the brain shows developmental changes. Neuronal synchronisation plays a role in seizure propagation (Shouse *et al.*, 1989; Drake *et al.*, 1991). Regional seizure susceptibility may vary depending on the synchrony manifested during sleep. Sleep spindles show distinct patterns in children under 3 years of age, displaying decreased spindle density and length (Nagata *et al.*, 1996; Scholle *et al.*, 2007). This decreased synchronisation may, in part, relate to maturational changes, that in turn may explain the decreased risk of seizures during sleep in infants.

### Changes in white matter maturation

Changes in myelination may account for different seizure patterns with age. Animal studies have demonstrated a lack of myelination may be associated with an increased risk of seizures (Emery *et al.*, 2009). Analogous findings are noted in children with genetic deletions (Nowakowska *et al.*, 2010). White matter maturation begins in the cerebellum, pons, and internal capsule. The frontal and temporal lobes are the last to complete myelination (Deoni *et al.*, 2011). These changes may play an important role in the variation of seizure phenotypes in infants, children, and adolescents.

### Receptor-ligand changes

Differential activity of circadian hormones and their receptors with age may further underlie changes in seizure susceptibility. Melatonin has a suppressive activity on $GABA_a$ receptors in the hippocampus (Stewart and Leung, 2005). GABA may be excitatory in immature neurons due to its paracrine accumulation and activity and is thought to play a role in neuronal migration (Khalilov *et al.*, 2005). GABA receptor concentration in epileptogenic foci has been found to be in sufficiently high concentrations to have a depolarising effect (Ben-Ari *et al.*, 2012). A gradual fall of melatonin concentration beginning from adolescence may play a secondary role in altering seizure susceptibility (Crowley *et al.*, 2012).

Other neuroendocrine factors, such as adenosine and cortisol, may modulate seizure activity with age (Boison, 2008). Basal forebrain adenosine concentration in rats has shown age-related changes, with increased accumulation of intracerebral adenosine following light exposure in older rats (Murillo-Rodriguez *et al.*, 2004). Similarly, physiological changes in human cortisol secretion have been noted to occur through the third year of life (Watamura *et al.*, 2004). The modulation of the activity of these neuroendocrine factors with increasing age may contribute to changes in seizure patterns.

### Limitations

Results should be interpreted in the context of data acquisition and analysis. The data from this study was collected from a tertiary care hospital and therefore may have been subjected to referral and information bias. Entrainment of the circadian rhythm may have occurred in response to inpatient rounds, meal services, and nursing visits. While adult studies were able to reproduce findings of diurnal seizure patterns in the outpatient setting, it is unclear if our findings apply to outpatients as well (Pavlova *et al.*, 2012). Patient antiepileptic treatment, notably medication reduction and discontinuation, during inpatient stay may have also affected seizure frequency and timing. We were not able to account for the effects of specific AEDs and their withdrawal on seizure activity. Our study relied on EEG localisation of seizures. Although we did not have a sufficient number of patients with seizure-free outcomes following surgical management, the gold-standard method of epilepsy localisation, video-EEG monitoring helped to improve localisation of seizures and document seizure timing. Further studies should be undertaken to establish a validation cohort in order to evaluate the findings of this study. Despite these limitations, our data are suggestive of important differences in seizure patterns among various age groups.

## Conclusion

EEG localisation plays an important role in determining the timing of seizures. The use of multiple variables, such as age and semiology, further improves the prediction of seizure occurrence and may provide new avenues for interventions (Loddenkemper, 2012). Further research, as attempted in pilot trials, may link these seizure patterns to circadian rhythm (Hofstra *et al*., 2011).

Prediction of seizure timing carries important implications. The knowledge of periods of greater risk is of value for patients and their caregivers. In addition, seizure prediction paradigms may allow for improved individualised treatments. Differential dosing regimens have shown improved seizure control in a randomised trial of 103 patients with subtherapeutic drug troughs (Yegnanarayan *et al*., 2006) and in a pilot trial of 17 patients with refractory nocturnal epilepsy (Guilhoto *et al*., 2011). Furthermore, a knowledge of the timing of seizures may help prevent injury and death during seizures. This study may serve as a first step to identify factors that influence seizure timing in different patient populations which may ultimately allow for improved management of seizures. □

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