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Melodie R. Winawer, Columbia University
Jerry Shih, Mayo Clinic
Erin S. Beck, Columbia University
Jessica E. Hunter, Kaiser Permanente Center for Health Research Northwest
Michael Epstein, Emory University
EPGP Investigators

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Genetic effects on sleep/wake variation of seizures

Melodie R. Winawer*,†, Jerry Shih‡, Erin S. Beck*, Jessica E. Hunter§,¶, Michael P. Epstein¶, and the EPGP Investigators†

*Department of Neurology, Columbia University, New York, New York, U.S.A
†G.H. Sergievsky Center, Columbia University, New York, New York, U.S.A
‡Department of Neurology, Mayo Clinic, Jacksonville, Florida, U.S.A
§Kaiser Permanente Center for Health Research Northwest, Portland, Oregon, U.S.A
¶Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia, U.S.A

Summary

Objective—There is a complex bidirectional relationship between sleep and epilepsy. Sleep/wake timing of seizures has been investigated for several individual seizure types and syndromes, but few large-scale studies of the timing of seizures exist in people with varied epilepsy types. In addition, the genetic contributions to seizure timing have not been well studied.

Methods—Sleep/wake timing of seizures was determined for 1,395 subjects in 546 families enrolled in the Epilepsy Phenome/Genome Project (EPGP). We examined seizure timing among subjects with different epilepsy types, seizure types, epilepsy syndromes, and localization. We also examined the familial aggregation of sleep/wake occurrence of seizures.

Results—Seizures in nonacquired focal epilepsy (NAFE) were more likely to occur during sleep than seizures in generalized epilepsy (GE), for both convulsive (odds ratio [OR] 5.2, 95% confidence interval [CI] 3.59–7.52) and nonconvulsive seizures (OR 4.2, 95% CI 2.48–7.21). Seizures occurring within 1 h of awakening were more likely to occur in patients with GE than with NAFE for both convulsive (OR 2.3, 95% CI 1.54–3.39) and nonconvulsive (OR 1.7, 95% CI 1.04–2.66) seizures. Frontal onset seizures were more likely than temporal onset seizures to occur during sleep. Sleep/wake timing of seizures in first-degree relatives predicted timing of seizures in the proband.
Significance—We found that sleep/wake timing of seizures is associated with both epilepsy syndrome and seizure type. In addition, we provide the first evidence for a genetic contribution to sleep/wake timing of seizures in a large group of individuals with common epilepsy syndromes.

Keywords
Genetics; Epilepsy; Seizure; Circadian; Sleep

Associations between epilepsy and sleep are complex and bidirectional. Sleep and lack of sleep can trigger seizures, and seizures and anticonvulsants may disrupt sleep architecture. Sleep and sleep deprivation also facilitate identification of interictal abnormalities on electroencephalography (EEG). Even in the absence of ongoing seizures, epilepsy may alter sleep.

Understanding the relationship between sleep and epilepsy can improve patient care. Knowledge of sleep/wake variation of seizures can direct the type and timing of antiepileptic medications, maximizing efficacy and minimizing adverse effects. Identifying epilepsy or seizure characteristics associated with sleep/wake patterns may help predict course and prognosis, and aid decisions about driving and timing of diagnostic procedures for greatest yield. Investigations into the biology of sleep and epilepsy may also facilitate discovery of more effective therapeutic strategies for patients with epilepsy. Increased recognition and treatment of sleep disorders in epilepsy such as obstructive sleep apnea (OSA), and of sleep/wake patterns of sudden unexpected death in epilepsy, can improve seizure control and quality of life, and may reduce mortality and morbidity.

Most current understanding of the relationship between sleep and epilepsy comes from animal data or small, primarily inpatient video-EEG studies over short periods. Few large studies exist on this topic and, to our knowledge, only one large questionnaire study of outpatients with common epilepsies. Few studies have examined genetic contributions to sleep/wake variation in epilepsy. Family members of patients with benign rolandic epilepsy with centrotemporal spikes (BECTS) have been shown to have interictal epileptiform discharges whose timing correlates with the timing of the seizures of family members, and some genetic syndromes, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), tend to manifest with seizures occurring at specific times in the sleep/wake cycle.

We examined sleep/wake occurrence of seizures in participants from the Epilepsy Phenome/Genome Project (EPGP), a multiinstitution study of genetic contributions to epilepsy in >4,000 participants with common epilepsy syndromes. EPGP participants reported on sleep/wake occurrence of seizures, allowing comparison of lifetime sleep/wake timing of seizures among many different epilepsy types within one study. EPGP inclusion criteria required participation by at least two affected individuals per family, allowing comparison of seizure timing in family members as a means to assess genetic contributions to sleep/wake variation of seizures.

We explored the relationship between sleep/wake state and seizure occurrence in EPGP participants, including the following: (1) association of seizure timing with broad epilepsy
type (generalized epilepsy [GE] vs. nonacquired focal epilepsy [NAFE]); (2) association of seizure timing with seizure type within GE and NAFE; (3) whether seizures that occur predominantly on awakening are specific to epilepsy syndrome or type; (4) how localization and lateralization correlate with sleep/wake occurrence of seizures; and (5) whether sleep/wake timing of seizures aggregates in families.

Methods

Epilepsy phenome/genome project (EPGP)

EPGP recruited, performed detailed phenotyping on, and collected DNA for genomic analyses from >4,000 participants with epilepsy.17 Participants were ascertained through screening patients and referrals at 27 clinical centers in the United States, Canada, Argentina, Australia, and New Zealand, and through a U.S. national recruitment campaign. Each clinical site collected sleep/wake variation of seizures, family history, electrophysiologic characteristics, neuroimaging findings, demographic variables, and response to anticonvulsant medications.

Part of EPGP focused on affected sibling pairs and parent–child pairs with epilepsy of unknown cause. These participants were required to have well-characterized GE or NAFE, but families were not required to be concordant for epilepsy type. The analysis presented here is restricted to GE and NAFE families. Each site’s institutional review board (IRB) approved the use of human subjects and all participants provided written informed consent.

Participants

This arm of the study required enrollment of at least an affected sibling pair or parent–child pair with epilepsy; in some cases, more than two relatives were enrolled. Individuals with only febrile or other acute symptomatic seizures were excluded, as were those with a history of acquired central nervous system injury before epilepsy onset. Individuals with autistic disorder, pervasive developmental disorder, or severe developmental delay before onset of seizures were also excluded. Potential participants were considered ineligible if they had an identified pathogenic mutation in a previously identified epilepsy gene.

To be classified as NAFE, patients had to have focal EEG abnormalities or unambiguous clinical semiology consistent with focal seizures. Neuroimaging could be normal, demonstrate nonspecific abnormalities unlikely to be the cause of epilepsy, or reveal mesial temporal sclerosis (MTS) or focal cortical dysplasia (FCD). MTS and FCD were not excluded because these lesions may have underlying genetic contributions. Participants with BECTS were not required to have neuroimaging.

To be classified as GE, participants had to have generalized onset seizures, normal neuroimaging if done, and generalized epileptiform EEG activity with a normal posterior dominant rhythm. The distribution of International League Against Epilepsy (ILAE) syndromes in EPGP GE/NAFE participants is shown in Table S1. (We used the 1989 Classification that was current when data collection began.)18
Data collection

Phenotypic information was collected using interviews and medical record abstraction. Participants with epilepsy were administered a detailed semistructured diagnostic interview to ascertain seizure types, semiology, seizure frequency, age at onset, history of status epilepticus, epilepsy syndrome, anticonvulsant response, and additional medical conditions. Specific questions assessed timing of seizures with respect to the sleep/wake cycle (Tables S2 and S3). We focused on sleep/wake timing (rather than time of day) to code seizure occurrence, as supported by prior studies.\textsuperscript{10} The interview was modified from a previously validated instrument.\textsuperscript{19,20} Basic laboratory data (e.g., serum antiepileptic drug [AED] levels), high-resolution magnetic resonance imaging (MRI) scans, EEG studies, and results of video-EEG telemetry were abstracted from the medical record. A blood sample was drawn from each participant and sent to the National Institute of Neurological Disorders and Stroke (NINDS) Human Genetics DNA and Cell Line Repository at the Coriell Institute for Medical Research for DNA extraction. Representative EEG and MRI studies were reviewed by EPGP’s Electrophysiology and Imaging Cores. Based on the collected information, the local site principal investigator completed final diagnoses including epilepsy type, seizure type, and ILAE syndrome.\textsuperscript{18} For children who were unable to answer interview questions, informant interviews were completed with a parent or caregiver. Children younger than 12 years who were able to answer questions did so with a caregiver present, whereas those aged 12 or older were permitted to answer interview questions either with or without a caregiver present. We restricted analysis to participants with either GE or NAFE, but not both, and with complete sleep/wake data for either convulsive or nonconvulsive seizures.

Sleep/wake timing of seizures—The EPGP Diagnostic Interview contained questions about timing of convulsive seizures (Table S2) and nonconvulsive seizures (Table S3). For seizures occurring during wakefulness, timing with regard to awakening was assessed.

Statistical analysis

For analysis, we dichotomized the multilevel variable (1 = asleep only, 2 = asleep mostly, 3 = equal, 4 = awake mostly, 5 = awake only) as: predominantly asleep (1 or 2) versus other (3, 4, or 5). We chose to dichotomize in this way because we believed that by self-report measure (i.e., rather than using epilepsy monitoring unit [EMU] data), having seizures only during sleep was more likely to be accurate than a reporting of having seizures only during wakefulness, since seizures during sleep could be more easily missed. However, as a sensitivity analysis, we also analyzed seizures as predominantly while awake (4 or 5) versus other (1, 2, or 3). We defined awake seizures as occurring on awakening if they occurred within 1 h after awakening from sleep, and as after awakening if they occurred >1 h after awakening from sleep. For analyses of seizures on awakening versus after awakening, we restricted the sample to seizures occurring while awake.

Based on self-report, seizures occurring during sleep are more likely to be recognized if they are convulsive rather than nonconvulsive. We therefore analyzed occurrence of convulsive versus nonconvulsive seizures separately and together. We also stratified by age (≤12 vs. >12 years), because younger children might be more likely to be observed at night by parents, and therefore have differential recognition of nocturnal seizures, and timing of seizure
occurrence might differ according to age. We used generalized estimating equations (GEE) models to compute odds ratios (ORs) with 95% confidence intervals (CIs), defining as the outcome predominantly asleep versus other, and as predictors epilepsy type (GE/NAFE), seizure type, ILAE syndrome, lateralization, and localization. GEE models were selected to adjust confidence intervals for the nonindependence of individuals within the same family. Age, sex, age at first seizure, and number of seizures were included in these models as covariates. We included number of seizures as a covariate because with increasing number of seizures, the likelihood of having all or the majority of seizures either during sleep or wakefulness would be expected to decrease simply by chance.

For assessment of familial aggregation of sleep/wake timing of seizures, we examined whether EPGP participants in the same family had the same sleep/wake status (predominantly sleep vs. other) more often than expected by chance. In EPGP, the “proband” was defined either as the first participant to be enrolled or the participant with the most detailed clinical information. We used the R package “gee” and SAS program PROC GENMOD to compute ORs and 95% CIs representing the degree to which the sleep/wake status in the other participant in the family (“relative”) predicted sleep/wake status in the proband. If the family contained more than two enrolled participants, we analyzed each pair separately, comparing each relative in the family with the proband. Results of proband pair analyses (“Proband pairs only”) are shown in Table 3b. Analyses were carried out within strata defined by family concordance of broad epilepsy type (all GE, all NAFE, or discordant). To account for potential bias resulting from our proband definition, we also repeated the analysis for all possible pairs without regard to the designated proband (“All family pairs,” Table 3a). Results of the two strategies were comparable.

Because many individuals had more than one type of nonconvulsive seizure, and each of these types might have a different sleep/wake pattern of occurrence, we approached the analysis of nonconvulsive seizures in two ways. In the first approach, we excluded individuals who had different sleep/wake status for different nonconvulsive seizure types. The remaining individuals were coded as “predominantly asleep” if all nonconvulsive seizures were predominantly asleep as described earlier, and “other” if all nonconvulsive seizure types were not predominantly asleep. In the second approach, we allowed multiple different outcomes within each individual. We show the outcome of the first analysis; the second produced comparable results.

We accounted for potential correlation of sleep/wake status of nonconvulsive seizures within individuals, and within the same family. This was required because outcomes in our dataset are potentially correlated for two reasons: (1) multiple observations may come from the same person (and therefore be correlated due to within-subject effects); or (2) multiple observations may come from relatives within the same family (and therefore be correlated due to shared polygenic or household effects).

Because some syndromes are defined by sleep/wake variation, in particular BECTS and frontal lobe epilepsy, we performed an additional set of analyses excluding BECTS and frontal lobe epilepsy in both individual-level and familial aggregation analyses.
Results

Included in the analysis were 1,395 EPGP participants (595 NAFE and 800 GE) (Table 1).

Sleep/wake variation of seizure occurrence by epilepsy type and seizure type

Epilepsy type (GE vs. NAFE) was a strong predictor of sleep/wake variation of seizure occurrence (Fig. 1), with seizures in NAFE more likely to occur during sleep than seizures in GE (OR 5.8, 95% CI 3.52–9.41); sensitivity analysis (asleep/equal vs. predominantly awake: OR 3.61, 95% CI 2.55–5.10). This relationship between epilepsy type and sleep-related seizure occurrence held for both convulsive (OR 5.2, 95% CI 3.59–7.52; asleep/equal vs. predominantly awake: OR 4.00, 95% CI 2.92–5.46) and nonconvulsive seizures (OR 4.2, 95% CI 2.48–7.21; asleep/equal vs. awake: OR 2.71, 95% CI 1.87–3.93) across all age groups. As predicted, convulsive seizures were more likely to be reported in sleep than nonconvulsive seizures (OR 3.6, 95% CI 2.24–5.88; asleep/equal vs. awake: OR 1.89, 95% CI 1.28–2.72).

Timing of seizures during wakefulness

We then explored timing of seizures during wakefulness (awakening vs. >1 h after awakening) in GE versus NAFE, and for convulsive versus nonconvulsive seizures (Fig. 2). Awake seizures were more likely to occur within 1 h of awakening in participants with GE than in participants with NAFE, for both convulsive (OR 2.3, 95% CI 1.54–3.39) and nonconvulsive (OR 1.7, 95% CI 1.04–2.66) seizures. After stratification by age, the significant effect persisted only in the >12 age group, for both convulsive and nonconvulsive seizures (convulsive: >12 years OR 2.4, 95% CI 1.53–3.70 vs. ≤12 years OR 1.7, 95% CI 0.46–6.01; nonconvulsive: >12 years OR 2.5, 95% CI 1.40–4.57 vs. ≤12 years OR 0.6, 95% CI 0.26–1.30).

Localization, lateralization, and ILAE syndrome

Sleep/wake patterns of seizure occurrence are considered to be characteristic of some localizations of focal epilepsy (particularly frontal and temporal) and specific epilepsy syndromes (e.g., juvenile myoclonic epilepsy [JME]), and may have accounted for the associations observed. To assess the relationship between timing of seizures and focal epilepsy localization, we collapsed focal ILAE syndromes to correspond to lobe of onset (e.g., frontal = 1,240 + 1,340 series; temporal = 1,210 + 1,310 series). Temporal onset seizures were less likely than frontal onset seizures to occur during sleep, but results were not significant (OR 0.3, 95% CI 0.06–1.10; asleep/equal versus predominantly awake: OR 0.43, CI 0.11–1.57). We also found that temporal onset seizures were significantly less likely to occur during sleep than seizures in BECTS (OR 0.2, 95% CI 0.05–0.52; asleep/ equal versus predominantly awake: OR 0.22, CI 0.07–0.68). We found no significant difference in sleep/wake patterns when comparing JME to either childhood absence epilepsy or juvenile absence epilepsy.

Familial aggregation of sleep/wake timing of seizures

For the analysis of familial aggregation of sleep/wake timing of seizures, we restricted analysis to probands and their siblings and parents who had either GE or NAFE, but not
both, and who had complete data for sleep/wake status. We removed participants who were unclassifiable or had missing data for key variables. We also removed participants who were second-degree relatives, and therefore “unlinked” to a proband, and participants who did not have an affected first-degree relative. This resulted in 1,058 participants for analysis in 515 families (Table 2). Sleep/wake timing in the relative predicted sleep/wake timing in the proband for both convulsive and nonconvulsive seizures (Table 3a and b). For convulsive seizures, significant evidence for familial aggregation of sleep/wake timing was restricted to pairs concordant for GE but not in those concordant for NAFE. For nonconvulsive seizures, ORs were greater in pairs concordant for NAFE than in pairs concordant for GE, but were significant in both groups.

We considered the possibility that the familial aggregation of sleep/wake occurrence might be explained by familial aggregation of syndrome or localization. For example, within focal epilepsies, familial aggregation of sleep/wake variation overall could be explained by familial aggregation of frontal lobe epilepsy and a tendency for frontal lobe seizures to occur during sleep. We therefore repeated the analysis excluding pairs concordant for familial syndromes known to have a sleep/wake pattern: frontal lobe syndromes and BECTS.

When pairs concordant for BECTS and frontal lobe epilepsy were excluded, familial aggregation of sleep/wake seizure occurrence persisted (Table 3c), in all pairs (GE + NAFE) and pairs concordant for NAFE. Using the same argument, that familial aggregation of sleep/wake variation in GE versus NAFE or within GE concordant pairs might result from familial syndromes with sleep/wake predominance, we repeated the analyses excluding generalized tonic–clonic seizures on awakening and JME. Familial aggregation was still observed after exclusions (all pairs: OR 3.29, CI 1.50–7.22; pairs concordant for GE: OR 1.54, CI 0.16–15.25).

Discussion

We identified clinical features predictive of sleep/wake occurrence of seizures in a large sample of individuals with common epilepsy syndromes. Our results indicate that seizures in generalized epilepsy—both convulsive and nonconvulsive—were less likely to occur during sleep than seizures in focal epilepsy. This is in keeping with prior reports of timing of focal seizures, although it varies with site of origin. For example, frontal lobe seizures are more likely to occur in sleep, particularly the early morning hours of sleep, whereas temporal lobe seizures are more likely to occur during wakefulness. In our study, temporal lobe seizures were also more likely to occur during wakefulness, and frontal lobe seizures more likely to occur during sleep, although the difference did not reach statistical significance with our sample size.

We also found that among seizures occurring during wakefulness, both convulsive and nonconvulsive seizures were more likely to occur within 1 h of awakening in individuals with GE than in those with NAFE. These results confirm the clinical observation of myoclonus on awakening in patients with JME, and are consistent with the characterization of the syndrome denoted generalized tonic–clonic seizures on awakening (GTCSA). However, these findings may have resulted from the tendency of clinicians to classify
individuals with these syndromes if seizures occurred on awakening. To account for this possible bias, we repeated the analysis excluding syndromes characterized by seizures on awakening, including JME and GTCSA. After exclusions, convulsive seizures were still more likely to occur on awakening in GE than in NAFE, although with a smaller effect size (without exclusion: OR 2.3, CI 1.54–3.39 vs. with exclusion OR 1.6, CI 1.06–2.41).

In EPGP, the effect of epilepsy type on the tendency for seizures to occur on awakening was observed only in individuals aged >12 years, which also corresponds to the observation of seizures on awakening in adolescent and adult-onset generalized epilepsy syndromes such as JME and generalized tonic–clonic seizures on awakening.

The biologic basis of on-awakening seizures in generalized epilepsy has been examined in human and animal studies. Transcranial magnetic stimulation identified increased cortical excitability early in the morning in patients with idiopathic generalized epilepsy, most prominent in JME. Human studies and animal models of idiopathic generalized epilepsies also demonstrate that transitions from sleep may constitute a vulnerable period for seizure occurrence, along with drowsiness and light slow wave sleep. Our finding that temporal lobe seizures are less likely than frontal lobe seizures to occur in sleep, although not significant, is in keeping with studies using video-EEG data. The largest non-EMU study also failed to find a significant difference in time of onset between these two seizure types. This may result from underidentification of seizures during sleep by self-report. We also found that seizures in BECTS were more likely to be nocturnal than in temporal lobe epilepsy (TLE), as observed previously. Again, this finding may have resulted from the clinical tendency to classify an individual as having BECTS if seizures were nocturnal. No other comparisons of sleep/wake patterns by ILAE syndrome reached statistical significance.

Our finding that temporal lobe seizures are less likely than frontal lobe seizures to occur in sleep, although not significant, is in keeping with studies using video-EEG data. The largest non-EMU study also failed to find a significant difference in time of onset between these two seizure types. This may result from underidentification of seizures during sleep by self-report. We also found that seizures in BECTS were more likely to be nocturnal than in temporal lobe epilepsy (TLE), as observed previously. Again, this finding may have resulted from the clinical tendency to classify an individual as having BECTS if seizures were nocturnal. No other comparisons of sleep/wake patterns by ILAE syndrome reached statistical significance.

The mechanism by which localization affects seizure timing is unclear, although intracortical inhibition in motor cortex may be abnormally decreased during non–rapid eye movement (REM) sleep in patients with frontal lobe epilepsy. During sleep, production of spindles is maximal in frontocentral areas; this may help explain the sleep predominance of frontal seizures. In a family study of nocturnal frontal lobe epilepsy (NFLE), parasomnias were found to be more frequent in relatives of patients with NFLE than in relatives of controls, suggesting shared abnormal, possibly cholinergic, and arousal systems. This finding also provides evidence for a genetic contribution linking epilepsy and sleep-related phenomena.

We found that convulsive seizures were more frequently reported in sleep than nonconvulsive seizures, but this may be because convulsive seizures are more likely to be noticed during sleep. However, this result may still reveal a fundamental biologic phenomenon; prior studies suggest that focal seizures occurring while sleep more frequently generalize compared to seizures that occur while awake.

Our results provide the first reported evidence for concordance of sleep/wake seizure timing in family members of individuals with common epilepsy syndromes, pointing to the importance of genetics underlying the biology of sleep/wake timing of seizures. Some prior
evidence for genetic contributions to sleep/wake variation of seizure occurrence stems from the observation that specific, relatively rare genetic epilepsy syndromes have specific sleep/wake patterns. In ADNFLE, frontal lobe seizures occur almost entirely during sleep.\textsuperscript{30} Mutations in the nicotinic acetylcholine receptor (nAChR), \textit{DEPDC5}, and \textit{KCNT1} have been identified in families with this disorder.\textsuperscript{31–33} It has been hypothesized that mutated nAChRs increase activity of arousal circuits, leading to seizures,\textsuperscript{34} and these mechanisms may affect sleep/wake variation of seizures. In BECTS, which is known to have genetic contributions,\textsuperscript{35} seizures are also predominantly nocturnal, and in 50\% of patients these seizures occur exclusively during sleep.\textsuperscript{36,37} In animal models, loss of sleep/wake “clock” genes may be associated with severe epilepsy; involvement of sleep/wake genes in human epilepsy has not been reported.\textsuperscript{38,39}

Several genes play a role in the suprachiasmatic nucleus in mammalian circadian rhythms,\textsuperscript{38} and loss of circadian transcription factors in mice has been shown to result in severe seizures.\textsuperscript{40} Circadian rhythmicity is controlled by transcription and translation of specific clock genes in a coordinated fashion. Ion channels and neurotransmitter receptors have also been demonstrated to be under circadian control, and the mammalian target of rapamycin (mTOR) signaling pathway has been proposed as a molecular link between epilepsy and sleep/wake biology.\textsuperscript{39} Electrical status epilepticus during slow wave sleep (ESES), a disorder in which slow wave sleep is replaced by epileptiform activity, has been linked to several genes including \textit{GRIN2A}\textsuperscript{41} and \textit{NCKSR2},\textsuperscript{42} suggesting another link between the biology of epilepsy and sleep.

EPGP provides a large and varied resource for examining sleep/wake variation of seizures and the familiality of that variation. However, several potential limitations exist. First, reliance on patient or informant reporting is likely to have resulted in underreporting of nonconvulsive seizures during sleep compared to convulsive seizures. For this reason, we separated analysis of convulsive and nonconvulsive seizures. In addition, sleep/wake timing was probably considered for final diagnosis in syndromes such as JME and BECTS. It is reassuring that when pairs concordant for BECTS and frontal lobe epilepsy were excluded, familial aggregation of sleep/wake seizure occurrence persisted, resolving concern that concordance of these syndromes was responsible for the observed familial aggregation.

A second limitation relates to the manner in which data on specific types of nonconvulsive seizures were collected. We asked participants to describe each of their seizure types, using an interview that contained questions about sleep/wake occurrence of each type. The final diagnosis of seizure types (e.g., myoclonic, absence, and complex partial) was made based on review of all collected information (interview, medical records, EEG, and MRI data). This approach did not allow us to link specific nonconvulsive seizure types established in the final diagnosis to self-reported information about sleep/wake occurrence of each nonconvulsive seizure type. This prevented reporting and analysis of sleep/wake variation of each nonconvulsive seizure type. In addition, because EPGP focused on familial epilepsies, all findings may not generalize to nonfamilial epilepsies. Finally, in EPGP we did not screen for sleep disorders such as OSA, which may be comorbid with epilepsy. Future studies would benefit from screening for this and related disorders.
Our discovery of familial aggregation of sleep/wake variation of seizures is informative in both clinical and research arenas. For patient care, it may provide useful data for counseling of families with multiple affected individuals with epilepsy, as temporal specificity of one family member’s epilepsy may help predict timing of seizures in other affected family members. It also presents novel possibilities for gene discovery in families, and suggests an aspect of phenotype definition that may help identify genetically homogenous subgroups for analysis. Better understanding of the biologic underpinnings of sleep/wake variation in epilepsy has great potential to improve patient care and inform innovative future research.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**Biography**

Melodie Rose Winawer is an Associate Professor of Neurology at Columbia University.

**References**


### Key Points

- Seizures in focal epilepsy are more likely than seizures in generalized epilepsy to occur during sleep.
- Frontal onset seizures are more likely than temporal-onset seizures to occur during sleep.
- Seizures that occur within 1 hour of awakening are more likely to occur in patients with generalized epilepsy than with focal epilepsy.
- There is familial aggregation of sleep/wake timing of seizures among first-degree relatives with epilepsy.
Figure 1.
Seizures in NAFE are more likely to occur during sleep than seizures in GE. This is true for both convulsive and nonconvulsive seizures. “Both” refers to analysis of combined convulsive and nonconvulsive seizures.
Epilepsia © ILAE
Figure 2.
Among seizures that occur while awake, seizures are more likely to occur within 1 h of awakening (“on awakening”) in subjects with GE (generalized onset) than with NAFE (partial onset), both for convulsive and nonconvulsive seizures.
Epilepsia © ILAE
### Table 1

**Participant demographics and seizure history**

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<tr>
<td>&gt;100</td>
<td>190</td>
<td>311</td>
<td>501</td>
<td></td>
</tr>
<tr>
<td>Missing/don’t know</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

*Limited to participants who had sleep/wake data for either convulsive or nonconvulsive seizures.*
Table 2
Family structure of 546 proband-family member pairs from 515 families with complete sleep/wake status in EPGP

<table>
<thead>
<tr>
<th>Pair type</th>
<th>N total</th>
<th>N both generalized</th>
<th>N both localized</th>
<th>N discordant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband + affected Parent</td>
<td>164</td>
<td>81</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>Proband + sibling</td>
<td>374</td>
<td>195</td>
<td>113</td>
<td>66</td>
</tr>
<tr>
<td>Proband + child</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>546</td>
<td>280</td>
<td>163</td>
<td>103</td>
</tr>
</tbody>
</table>
Table 3

Familial aggregation of sleep/wake seizure occurrence\(^a\). a1. All family pairs (predominantly asleep vs. other).
a2. All family pairs sensitivity analysis (predominantly awake vs. other). b1. Proband pairs only (predominantly asleep vs. other). b2. Proband pairs only sensitivity analysis (predominantly awake vs. other). c1. Proband pairs: Excluding pairs concordant for BECTS and frontal (predominantly asleep vs. other). c2. Proband pair’s sensitivity analysis: Excluding pairs concordant for BECTS and frontal (predominantly awake vs. other).

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>All pairs</th>
<th>Concordant GE</th>
<th>Concordant NAFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsive</td>
<td>3.2 (1.91–5.25)</td>
<td>2.0 (1.07–3.64)</td>
<td>0.81 (0.16–4.11)</td>
</tr>
<tr>
<td>Nonconvulsive</td>
<td>9.7 (3.94–23.69)</td>
<td>4.6 (1.61–12.84)</td>
<td>18.6 (2.75–125.57)</td>
</tr>
<tr>
<td>Convulsive and nonconvulsive combined</td>
<td>13.9 (7.35–26.36)</td>
<td>6.1 (2.84–13.08)</td>
<td>7.3 (0.74–72.92)</td>
</tr>
<tr>
<td>a2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsive</td>
<td>3.45 (1.88–6.32)</td>
<td>2.21 (0.97–5.06)</td>
<td>1.88 (0.61–5.88)</td>
</tr>
<tr>
<td>Nonconvulsive</td>
<td>8.67 (3.87–19.41)</td>
<td>4.40 (1.32–14.68)</td>
<td>16.01 (4.56–56.14)</td>
</tr>
<tr>
<td>Convulsive and nonconvulsive combined</td>
<td>8.07 (3.99–16.33)</td>
<td>6.1 (2.10–17.66)</td>
<td>7.1 (2.55–19.82)</td>
</tr>
<tr>
<td>b1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsive</td>
<td>3.9 (1.85–8.11)</td>
<td>1.4 (0.14–14.05)</td>
<td>2.18 (0.89–5.33)</td>
</tr>
<tr>
<td>Nonconvulsive</td>
<td>9.4 (2.58–34.51)</td>
<td>40.0 (4.35–367.22)</td>
<td>3.7 (0.60–22.52)</td>
</tr>
<tr>
<td>Convulsive and nonconvulsive combined</td>
<td>15.0 (5.57–40.54)</td>
<td>14.8 (0.55–397.69)</td>
<td>5.9 (1.78–19.39)</td>
</tr>
<tr>
<td>b2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsive</td>
<td>3.35 (1.81–6.22)</td>
<td>2.18 (0.95–5.02)</td>
<td>1.92 (0.60–6.15)</td>
</tr>
<tr>
<td>Convulsive and nonconvulsive combined</td>
<td>7.93 (3.85–16.34)</td>
<td>5.97 (2.07–17.25)</td>
<td>6.63 (2.18–120.17)</td>
</tr>
<tr>
<td>c1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsive</td>
<td>3.6 (1.71–7.80)</td>
<td>1.4 (0.14–14.05)</td>
<td>1.9 (0.76–4.92)</td>
</tr>
<tr>
<td>Nonconvulsive</td>
<td>10.2 (2.80–37.29)</td>
<td>40.0 (4.35–367.22)</td>
<td>4.0 (0.65–24.40)</td>
</tr>
<tr>
<td>Convulsive and nonconvulsive combined</td>
<td>12.7 (4.39–36.47)</td>
<td>14.8 (0.55–397.69)</td>
<td>4.8 (1.30–17.65)</td>
</tr>
<tr>
<td>c2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsive</td>
<td>3.24 (1.73–6.06)</td>
<td>1.98 (0.84–4.68)</td>
<td>1.92 (0.60–6.15)</td>
</tr>
<tr>
<td>Nonconvulsive</td>
<td>9.07 (3.93–20.93)</td>
<td>4.67 (1.37–15.95)</td>
<td>16.62 (4.31–64.11)</td>
</tr>
<tr>
<td>Convulsive and nonconvulsive combined</td>
<td>7.52 (3.59–15.75)</td>
<td>5.34 (1.79–15.93)</td>
<td>6.63 (2.18–20.17)</td>
</tr>
</tbody>
</table>

\(^a\) Odds ratios and 95% confidence intervals for association of proband’s (outcome) sleep/wake status with relative’s (predictor) sleep/wake status, dichotomized as predominantly sleep versus other. As a sensitivity analysis, we also performed the same analyses dichotomizing sleep/wake status as predominantly awake versus other. In 3a1 and 3a2, all family pairs are analyzed. In 3b1 and 3b2, the analyses were performed only for pairs including the proband. For instance, in a family with a parent and two children in which one child was the proband, in the proband analysis there would be only two pairs: proband-sib and proband-parent. In the All pairs analysis there would be three pairs included, one sib-sib pair and two parent-child pairs. For 3c1 and 3c2, BECTS and frontal lobe seizures were excluded from the Proband pairs analyses. Covariates included age, age at first seizure, and number of seizures. ORs could not be calculated for pairs that were discordant for GE/NAFE because none of these pairs had both relatives with seizures predominantly during sleep. Therefore, pairs discordant for GE/NAFE were excluded.