Relationship of Epileptic Seizures to Sleep Stage and Sleep Depth

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A CRITICAL QUESTION IN EPILEPSY RESEARCH IS HOW SEIZURES ARE INITIATED AND PROPAGATED UNDER CERTAIN PHYSIOLOGIC CONDITIONS. Study of these conditions may contribute to developing new treatments for this disorder. One of these conditions is sleep, particularly NREM sleep. Interictal epileptiform discharges (IEDs) are sharp waves in the electroencephalographic (EEG) background occurring between seizures that correlate with depolarization of the neuronal membrane. These IEDs are generally activated by NREM sleep and relatively suppressed by REM sleep. In temporal lobe epilepsy, IEDs appear to be more common in deeper stages of NREM sleep (stages 3 and 4). Using the change in log delta power as a measure of deepening sleep, Malow and colleagues also found that IEDs occurred more frequently as sleep deepened and closer to sleep onset.

In contrast to IEDs, the relationship of seizures to sleep has not been well characterized. Several studies have noted that seizures are more common during NREM sleep, especially NREM stage 2 sleep. With the exception of Herman and colleagues investigators have not performed continuous overnight video-EEG polysomnography (VPSG) to accurately score sleep stages and to account for the proportion of time spent in each sleep stage. Determining the proportion of time spent in each sleep stage allows for calculation of seizure rates (seizures per hour of sleep). Seizure rates convey a more accurate measure of which sleep stages show the highest association with seizures because time spent in each stage is accounted for.

In this study, we examined the relationship of seizures to sleep in patients with epilepsy undergoing overnight continuous VPSG. To better generalize our findings to epilepsy patients as a whole, we included two distinct sets of patients in our analysis. These two groups consisted of: (1) adults with medically refractory epilepsy undergoing presurgical evaluations in our epilepsy laboratory who were monitored with electroencephalography (EOG) and chin electromyography (EMG) to stage sleep and (2) adults and children with epilepsy undergoing PSG in our sleep laboratory for a variety of clinical and research indications. Our goal was to determine if seizures resemble IEDs in their relationship to sleep.

INTRODUCTION

METHODS

Patients

This study was approved by the University of Michigan Institutional Review Board. We identified epileptic seizures recorded on overnight studies by reviewing the records of all epilepsy patients undergoing VPSG at the University of Michigan in the sleep laboratory, January 1985 to December 2000 or the adult epilepsy laboratory, July 1998 to June 2000.

Data in the sleep laboratory were collected from adult and pediatric patients who had undergone 1 to 2 nights of overnight continuous VPSG, performed for various clinical (eg, evaluation for sleep-related breathing disorders, characterization of nocturnal events) or research indications (eg, the relationship of IEDs to sleep). A portion of the sleep laboratory studies were performed in the General Clinical Research Center. The EEG coverage ranged from 4 channels (central to ear and central to occipital derivations) to 21 channels placed using the 10-20 system. Monitoring of EOG and chin EMG are standard in our sleep laboratory for sleep scoring. Because of the variable EEG coverage and the lack of a comprehensive presurgical evaluation in the sleep laboratory patients, temporal versus extratemporal localization of their epileptogenic regions could not be definitively determined. All patients had partial or secondary generalized seizures except for one patient who had tonic seizures and whose NREM sleep could not be differentiated into stages because of almost continuous interictal epileptiform activity. Because this patient had generalized seizures, while all others had partial seizures, and because of the inability to differentiate NREM sleep stages, we excluded this patient from our analysis. Patients in the sleep laboratory did not have their antiepileptic drugs (AEDs) altered prior to or during...
Data in the epilepsy laboratory were collected exclusively from a cohort of adult patients admitted for presurgical evaluations. Length of inpatient monitoring varied between 3 and 8 days. All patients were tapered off all AEDs during monitoring using standard guidelines in our laboratory. These guidelines recommend that the AED with the longest half-life is decreased by 25% of the original dose 2 days prior to admission, by 50% 1 day prior to admission, and discontinued 3 days after monitoring began. Individual physician discretion was allowed with these guidelines, depending on individual history (eg, history of convulsive status epilepticus, severity of seizures, treatment with barbiturates), although physicians were asked to taper drugs similarly regardless of patients' sleep deprivation status. All patients participated in a structured sleep protocol, in which they were instructed to sleep every night or every other night between 10 pm and 6 am. Half of the cohort of 84 patients were randomly assigned to sleep deprivation every other night as part of a research protocol to determine the effects of sleep deprivation on seizure frequency. Only 1 patient received benzodiazepines for seizure clusters during 1 night of his VPSG.

All epilepsy laboratory patients underwent continuous video-EEG monitoring (Grass Telefactor, West Conshohocken, PA, USA) as part of their epilepsy surgery evaluation. The standard 10-20 system was implemented along with sphenoidal electrodes. Extratemporal electrode coverage was also used as clinically indicated. Additionally, EOG and chin EMG channels were included to score sleep. The EEG was digitized using 200 Hz, and filter settings were set at 0.3 Hz and 70 Hz. For sleep scoring, analog data stored on videotapes were transferred into a digital EEG system (Grass Telefactor, West Conshohocken, PA, USA). To define temporal versus extratemporal localization of the epileptogenic region, we used a combination of all of the data available, including clinical characteristics and scalp-EEG recordings (all patients), invasive monitoring recordings (5% of patients), brain MRI results (all patients), and surgical outcome results (54% of patients).

### Sleep scoring and identification of seizures

Each patient's recording was partitioned into epochs of 30 seconds for sleep scoring. Visual scoring was performed using Rechtschaffen and Kales criteria for recordings performed in the sleep laboratory. For recordings performed in the epilepsy laboratory, in which C3-A2 was not available, we used four channels, predominantly C3-O1 and C4-O2, with reference as needed to Fp1-C3 and Fp2-C4. NREM stages 3 and 4 were combined into one stage (3-4), as is the practice of our clinical laboratory. All records were scored by MM, a registered polysomnographic technologist. Records and reports were reviewed to determine seizure onset times and to characterize the nature of the events (eg, partial versus secondarily generalized, clinical versus subclinical). Seizures not associated with electrographic changes were excluded. As surface electrodes may not detect seizure onsets, seizures beginning within 30 seconds after an arousal from established sleep were included.

### Analysis of change in sleep depth prior to a seizure

In the epilepsy patients, log delta power (LDP), a measure of the depth of sleep, was calculated using the fast Fourier transform (FFT). It was used as a continuous measure of sleep depth using an algorithm provided by Grass Telefactor (West Conshohocken, PA, USA). The data were reduced by eliminating alternate sample points, padded with 28 zeros on each side, and then multiplied by a Hanning window to obtain the FFT for 2-second segments. Half-overlapping windows were applied. The frequency resolution was 0.39 Hz. Delta power was calculated by summing the power in the delta frequency range, between the 0.79 and the 3.9 Hz bin. Delta power was then averaged over 30 seconds, and LDP was calculated by multiplying the log base 10 of the delta power by a factor of 10. Analysis was limited to seizures in which patients had been asleep for at least 10 minutes before the seizure in order to have enough data to detect a trend. The LDP analysis included 25 seizures in 15 patients.

### Statistical Analysis

All statistical analyses were done using the SAS statistical package (SAS Institute, Inc., Carey, NC, USA). For all statistical tests, the level of significance was set at $\alpha = 0.05$. The distribution of seizures across NREM and REM sleep was determined while adjusting for the time spent in each sleep stage. Seizure rates for each stage were calculated by adding the number of seizures in each stage and dividing by the total amount of sleep spent in that stage. Paired t-tests were performed to compare seizure rates in different stages of sleep. Separate analyses were performed in sleep laboratory and epilepsy laboratory patients, and those with single and multiple seizures in 1 night.

Nine nights of sleep in 9 patients (1 from the sleep laboratory and 8 from the epilepsy laboratory containing a total of 15 seizures) did not contain all sleep stages. Four nights lacked NREM stage 3, 4 nights lacked REM, and 1 night lacked both NREM stage 3 and REM sleep. Including these nights might have biased our results toward higher seizure rates in NREM stages 1 and 2. This is because there was no opportunity for seizures to occur during NREM stage 3 or REM sleep when that stage of sleep did not occur. Therefore, in the main analysis, we excluded these 9 nights of sleep. Three of these seizures occurred during NREM stage 1 sleep, 9 during NREM stage 2 sleep, and 3 during NREM stage 3 sleep. To ensure that we were not introducing a different bias by excluding these seizures, we ran separate analyses including these seizures and achieved similar findings that are presented in the results section.

The time of night was divided into quartiles according to each patient's length of sleep. Time of night was defined as time from sleep

### Table 1—Seizure Rates in Different Stages of Sleep (number of seizures per hours of each sleep stage)

<table>
<thead>
<tr>
<th>Sleep Laboratory Patients</th>
<th>NREM Stage 1</th>
<th>NREM Stage 2</th>
<th>NREM Stage 3-4</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.32</td>
<td>0.40*</td>
<td>0.38</td>
<td>0.10</td>
</tr>
<tr>
<td>Epilepsy Laboratory Patients</td>
<td>0.35*</td>
<td>0.37*</td>
<td>0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>Combined Groups</td>
<td>0.34*</td>
<td>0.38*</td>
<td>0.29*</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Higher seizure rate compared to REM sleep ($p < 0.05$) in that particular group of laboratory patients. See text for detailed p-values.
onset to time of final awakening. The number of seizures that occurred in each quartile of the night was determined. All seizures were included in this analysis. These data were analyzed using a chi-square test of equal proportions.

Chi-square and two-sample t-tests were performed to determine if epilepsy patients with single and multiple seizures during sleep differed according to clinical characteristics (eg, age, gender, seizure localization). Chi-square tests were performed to determine whether patients with seizures during sleep were more likely to have temporal or extratemporal/nonlocalizable epileptogenic regions. Two-sample t-tests were performed to determine if the relative proportion of sleep stages differed among those in the epilepsy laboratory and the sleep laboratory, and those with single versus multiple seizures during sleep.

A linear mixed model was applied to the data to test whether LDP changed significantly within the 10 minutes of sleep preceding a seizure. Since our study involved taking repeated measurements of LDP over time from the same subject, correlated observations were introduced, as any set of observations from the same subject are not independent of each other. Therefore, adjustments for these correlations were also included in the model. We used a compound symmetry correlation matrix, which assumes that any two observations are equally correlated regardless of how far apart in time they were.²

RESULTS

Given the inherent differences between groups, our results are presented separately for the sleep and epilepsy laboratory patients and then for the groups combined.

Sleep Laboratory Patients

Twenty-three patients from the sleep laboratory, aged 6 to 72 years (25.7 ± 16.7, mean ± standard deviation) contributed 50 sleep-related seizures (42 partial, 8 secondarily generalized). Seven seizures were subclinical (eg, EEG correlate of a seizure without clinical manifestations), and all of these were multiple seizures (more than 1 a night). Ninety-four percent of seizures occurred in NREM sleep (16% in stage 1, 58% in stage 2, and 20% in stage 3-4), and 6% in REM sleep.

Seizure rate (number of seizures divided by the hours spent in each sleep stage) was calculated for nights of sleep that contained all sleep stages (1 = NREM sleep stage 1; 2 = NREM sleep stage 2; 3,4 = NREM sleep stage 3-4 combined; R = REM sleep stage) for nights of sleep that contained all sleep stages as described in the Methods section. Seizure rate was higher in NREM sleep compared to REM sleep (p = .0004), with seizure rates for each sleep stage listed in Table 1. Specifically, NREM stage 2 sleep had a higher seizure rate than did REM sleep (p = .011), and NREM stage 3-4 sleep had a marginally higher seizure rate than did REM sleep (p = .052). Of the 23 patients, 12 contributed 13 single seizures (eg, only 1 seizure recorded in a night) and the other 11 patients contributed 37 multiple seizures (eg, 2 or more seizures recorded in 1 night). Single seizures were more likely to occur out of NREM stage 2 compared to NREM stage 3-4 (p = .047). Among multiple seizures, no significant differences among NREM sleep stages were found. Seizures were not more likely to occur in any quartile, including the first quartile of the night. When seizures occurred during REM sleep, they did not occur at a time of transition into or out of REM sleep.

Table 2—Sleep Architecture (percentage of time spent in each sleep stage)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NREM Stage 1</th>
<th>NREM Stage 2</th>
<th>NREM Stage 3-4</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Laboratory Patients</td>
<td>15%</td>
<td>50%</td>
<td>21%*</td>
<td>14%</td>
</tr>
<tr>
<td>Epilepsy Laboratory Patients</td>
<td>17%</td>
<td>59%</td>
<td>10%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Only nights containing all stages of sleep are included in this table.

*Higher NREM Stage 3-4 proportion compared to epilepsy laboratory patients

Epilepsy Laboratory Patients

Thirty-two patients from the epilepsy laboratory, aged 19 to 57 years (41.7 ± 10.1) contributed 67 sleep-related seizures (51 partial and 16 secondarily generalized). Nine seizures were subclinical, and 8 of these were multiple seizures (more than 1 a night). Ninety-five percent of seizures occurred in NREM sleep (18% in stage 1, 62% in stage 2, 15% in stage 3-4), and 5% in REM sleep.

Seizure rate was higher in NREM sleep as compared to REM sleep (p = .004), with seizure rates for each sleep stage listed in Table 1. Specifically, NREM stage 1 had a higher seizure rate than did REM sleep (p = .028) and NREM stage 2 had a higher seizure rate than did REM sleep (p = .008). Of the 32 patients, 19 contributed 22 single seizures and 13 contributed 45 multiple seizures. Single seizures were more likely to occur out of NREM stage 1 compared to stage 3-4 sleep (p = .015), and NREM stage 2 compared to stage 3-4 sleep (p = .0025). Among multiple seizures, the seizure rate was higher in NREM stage 2 than stage 1 sleep (p = .023). Seizures were not more likely to occur in any quartile, including the first quartile of the night. When seizures occurred during REM sleep, they did not occur at a time of transition into or out of REM sleep.

Sleep and Epilepsy Patients Combined

Fifty-five patients from the sleep and epilepsy laboratories combined contributed 117 seizures (93 partial and 24 secondarily generalized). Sixteen seizures were subclinical. Ninety-five percent of seizures occurred in NREM sleep (61% in stage 2, 20% in stage 1, 14% in stage 3-4), and 5% in REM sleep.

Seizure rate was higher in NREM sleep compared to REM sleep (p = .004). Figure 2 illustrates the proportion of seizures during sleep. Table 3 presents the characteristics of epilepsy laboratory patients with single vs. multiple seizures during sleep.

Table 3—Characteristics of Epilepsy Laboratory Patients with Single vs. Multiple Seizures during Sleep

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single seizures during sleep (n = 19)</th>
<th>Multiple seizures during sleep (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.3 ± 9.6</td>
<td>40.9 ± 11</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender (women)</td>
<td>9 (47%)</td>
<td>6 (43%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Localization: Temporal</td>
<td>12 (63%)</td>
<td>8 (57%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Lesional</td>
<td>15 (79%)</td>
<td>11 (79%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Frequency (Seizures/month)</td>
<td>11.8 ± 9.8</td>
<td>15.6 ± 19.1</td>
<td>0.51</td>
</tr>
<tr>
<td>Age at Seizure Onset</td>
<td>14.9 ± 11.5</td>
<td>18.6 ± 13.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Years of Seizures</td>
<td>27.3 ± 14.2</td>
<td>22.3 ± 15.5</td>
<td>0.35</td>
</tr>
<tr>
<td>Assigned to Sleep Deprivation</td>
<td>6 (32%)</td>
<td>6 (43%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Subclinical Seizures</td>
<td>1 (5%)</td>
<td>8 (18%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>
with seizure rates for each sleep stage listed in Table 1. Each NREM sleep stage had a significantly higher seizure rate compared to REM sleep (Figure 1). Among NREM sleep stages, the rate of seizures was highest in NREM stage 2 sleep followed by NREM stage 1 sleep, although differences in rates among NREM sleep stages were not statistically significant. Seizure rates for single versus multiple seizures recorded in 1 night were then analyzed separately. For the single seizures, seizure rate was highest in NREM stage 1, followed by NREM stage 2, then by REM, and finally by NREM stage 3-4 sleep (Figure 2). Statistically significant differences in single seizure rates were noted between NREM sleep stages 1 compared to 3-4 and between stages 2 compared to 3-4. For the multiple seizures, differences among NREM sleep stages did not reach statistical significance (p > 0.10).

Analysis including all nights of sleep

As discussed in the Methods section, we ran our main analysis excluding the 9 nights of sleep that did not contain all sleep stages. As a confirmation of our results, we included all nights of sleep in a separate analysis and found that seizure rates were even more significant in NREM stages 1 (p = 0.002) and 2 (p = 0.0001) and at the same level of significance in NREM stages 3-4 (p = 0.045) compared to REM sleep. Table 4 presents the seizure rates in different stages of sleep for each group of patients and for the patients combined, including all of the nights of sleep, and demonstrates that the two analyses produce comparable results. For the epilepsy patients, seizure rates remained significant for NREM stages 1 (p = 0.001) and 2 (p = 0.004) compared to REM sleep. For the sleep patients, seizure rates remained significant for NREM stage 2 (p = 0.006) compared to REM sleep.

Differences between patients with single and multiple seizures

Given the observed difference in statistical significance between single and multiple seizures for seizure rate in NREM sleep stages, the biologic characteristics of single and multiple seizure patients were then compared. We analyzed the effects of age and gender as predictors of single versus multiple seizures in our sleep laboratory and epilepsy laboratory patients individually and combined and did not find a statistically significant difference between the two groups (p > 0.10). We did find that subclinical seizures were more frequent in patients with multiple seizures (p = 0.026). We then examined the presence of subclinical seizures as well as the effects of seizure localization, seizure frequency, age of onset, and years of seizures as predictors of single versus multiple seizures in our epilepsy laboratory patients and did not find statistically significant differences in any of these variables (Table 3). Because most of the sleep laboratory patients were not presurgical candidates, consistent information was not available on seizure localization, seizure frequency, age of onset, and years of seizures, and, therefore, these analyses were limited to the epilepsy laboratory patients.

<table>
<thead>
<tr>
<th>Table 4—Seizure Rates in Different Stages of Sleep (number of seizures per hours of each sleep stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Laboratory Patients</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Epilepsy Laboratory Patients</td>
</tr>
<tr>
<td>Combined Groups</td>
</tr>
</tbody>
</table>

All nights of sleep were included in this Table.

*Higher seizure rate compared to REM sleep (p < 0.05) in that particular group of laboratory patients. See text for detailed p-values.

Relationship of seizure localization to the occurrence of seizures during sleep

Of the 32 epilepsy laboratory patients with seizures during sleep, 19 (59%) had epileptogenic regions localized to the temporal lobe, and 13 (41%) had either extratemporal or nonlocalizable epileptogenic regions. Patients with seizures during sleep were not more likely to have a temporal as compared to an extratemporal/nonlocalizable epileptogenic region (p > 0.10).

Sleep architecture

Both sleep laboratory and epilepsy laboratory patients had increased proportions of NREM stage 1 sleep compared to normative values.13 The only significant difference between the two groups of patients was in the proportion of NREM stage 3-4 sleep, which was higher in the sleep laboratory patients (p < 0.0006). This may be accounted for by the relatively older age of the epilepsy laboratory patients. The relative proportions of sleep stages are listed in Table 2. Proportions of stages did not differ among those with single versus multiple seizures in one night.

Log delta power analysis

The LDP increased significantly in the 10 minutes before a seizure (p < .003). A representative patient is shown in Figure 3. Average time from sleep onset to each seizure was 24.7 minutes ± 22.5 (mean ± standard deviation; range 10-106 minutes).

DISCUSSION

The relationship between epileptic seizures and sleep has intrigued clinicians and scientists since antiquity, when Aristotle observed that epilepsy often begins during sleep,14 and remains a fascinating topic of research and dilemma. Most reports suggest that NREM sleep, especially NREM stage 2 sleep, facilitates seizures and REM sleep suppresses them.4,7 Adjustment for the time spent in REM versus NREM sleep, and within different stages of NREM sleep, however, had not been previously performed with the exception of the study of Herman et al.7 Therefore, a direct comparison of the seizure frequency in each sleep state and stage had not been examined thoroughly in prior studies. As NREM stage 2 sleep generally comprises the majority of time spent asleep, we believe it is essential to adjust for the proportion of time spent in sleep stages in such an analysis. Because all of our patients had overnight continuous video-EEG recordings with sleep staging, we were able to calculate seizure rates, thereby adjusting for the time spent in various NREM sleep stages and in REM sleep. Therefore, our study adds a new dimension of information to the literature on seizure occurrence...
sleep. Because we included patients from two distinct laboratory
ries and found similar results, we feel confident generalizing our data to
epilepsy patients overall.

We found that epileptic seizures during sleep resemble IEDs in being
more common in NREM than in REM sleep. In contrast, while IEDs
predominate during deeper stages of sleep, at least in most reports of
partial epilepsy,2315,16 seizures are more frequent during lighter stages of
sleep. For the sleep and epilepsy laboratory data combined, at least for
seizures that occur isolated in a night, light NREM sleep (stages 1 or 2
or both) has the highest rate of epileptic seizures. Seizures are not more
likely to occur in the first quartile of the night, in contrast to IEDs.1
These findings hold across all patients as well as in two distinct sub-
groups of patients (eg, adults and children in the sleep laboratory and
medically refractory adult epilepsy patients in the epilepsy laboratory).
Applying LDP as a measure of sleep depth in a subgroup of epilepsy
patients, we found that sleep deepens just prior to seizure occurrence.
This is consistent with observations by Malow and colleagues,3 who pre-
viously found that IEDs were more common as sleep was deepening.

These findings suggest that neurophysiologic processes involved in
the deepening of NREM sleep may facilitate both seizures and IEDs,
even though the exact level of sleep depth that is maximally facilitating
probably differs for seizures and IEDs. NREM sleep represents a state of
synchronization between the brainstem reticular activating system, thala-
ampus, and cortex (pyramidal neurons). This concept has been charac-
terized by Steriade and colleagues using simultaneous recordings from
thalamus, thalamocortical projection neurons, and pyramidal neurons in
anesthetized cats. In contrast, REM sleep and wakefulness, two brain-
activated behavioral states, are opposed to the resting EEG-synchronized
sleep.17 The generation of REM sleep is associated, at least partially, by
the disinhibition of mesopontine cholinergic cells, resulting in an
increased brainstem cholinergic input to thalamocortical neurons, pro-
ducing a relative state of cortical activation. This neurochemical
dichotomy between NREM and REM sleep may explain why seizures
and IEDs are relatively activated by NREM sleep and are relatively sup-
pressed by REM sleep. Steriade and colleagues have also shown that the
process of deepening NREM sleep is associated with removal of acetyl-
choline and progressive hyperpolarization of thalamocortical neurons.
The critical level of hyperpolarization for activating epileptic seizures
versus IEDs has not been established in experimental models and awaits
further investigation. Varying levels of hyperpolarization may facilitate
IEDs and seizures. Previous work examining the relationship of IEDs to
seizures has shown that IEDs do not increase prior to seizures during
sleep, supporting that these phenomena are activated preferentially.18

Based upon our work and those of others showing that seizures are
more prevalent in lighter stages of sleep, yet as sleep is deepening with-
in these lighter stages, we propose the following model. Arousals from
sleep result in transitions to lighter sleep, followed by a return to deper-
level of sleep. On the descent back into deeper levels of sleep, seizures
are more likely to occur. This model is consistent with work showing
that patients with epilepsy have impaired sleep continuity, with more
fragmentation of sleep given frequent awakenings, even in the absence
of seizures or antiepileptic drugs.19 Therefore, epilepsy patients may be
more susceptible to the neurophysiologic changes associated with sleep-
stage transitions. Our proposed model may also explain why patho-
physiologic processes that fragment sleep, such as obstructive sleep
apnea (OSA), have been associated with worsening seizure control, and
why treatment of these disorders may potentially improve seizure con-
trol.20,22 In one series, those with medically refractory epilepsy and OSA
were more likely to have seizures during sleep than those without OSA,
supporting the premise that processes that fragment sleep facilitate
seizures.23 The literature also suggests that antiepileptic drugs may exert
their beneficial actions on seizures not only via direct effects on neuronal
excitability, but also via stabilization of sleep and reduction of sleep-
stage transitions. In one study, carbamazepine given to patients with
newly diagnosed epilepsy improved sleep efficiency and decreased
arousals from sleep on seizure-free nights. These subjects had impaired
sleep efficiency and increased arousals compared to nonepileptic con-
trols.24 This model will need to be tested more extensively in studies
examining the relationship of seizures to sleep-stage transitions and
other measures of variability in sleep architecture.

Our results are consistent with those of Herman and colleagues, who
also found that seizure rate was highest in light NREM sleep.7 This
group was the first to examine seizure rates and laid the groundwork for
our investigation. Although statistical significance was achieved in their
study for seizures being more common in NREM sleep than in REM
sleep, the rate of seizures in NREM stages 1 or 2 sleep in their study was
not statistically significant compared with other NREM sleep stages.
However, subgroups of patients with single and multiple seizures during
sleep were not analyzed separately and continuous VPSG with sleep
staging was available only in those with temporal lobe epilepsy. Our
finding of differences in seizure rates between those with single and
multiple seizures raises the possibility that these two subgroups are bio-
logically different. For example, seizures occurring multiple times a
night, as opposed to once in a night, were more likely to be subclinical.
These multiple seizures may also be indicative of more active epileptic
foci within the brain. For example, these foci may be more autonomous
and less influenced by sleep stage than are foci giving rise to isolated
(single) seizures. Although gender, age, age at seizure onset, years of
seizures, seizure frequency, seizure localization, or presence of a lesion
did not differ significantly among those with single or multiple seizures
during sleep, larger cohorts of patients will be necessary to fully address
this issue of biologic differences between the two groups. An alterna-
tive explanation for why we found that seizure rates during lighter stages
of NREM sleep were statistically significant in the single-seizure group
but not in the multiple-seizure group is that multiple seizures altered
sleep architecture, thereby confounding our analysis of this effect.

We also found that the majority of patients with seizures during sleep,
including those with multiple seizures in 1 night, had temporal lobe
epileptogenic regions as opposed to extratemporal or nonlocalizable
epileptogenic regions (59% vs. 41%). Herman and colleagues reported
that patients with frontal lobe epilepsy were more likely to have a large
percentage of seizures during sleep compared to those with other types
of epilepsy (eg, mesial temporal, neocortical, and occipital).7 Very few
of our patients undergoing presurgical evaluations had intracranial mon-
toring, and only 54% had surgical resections, with the majority having
resection of both mesial and neocortical structures. Therefore, we were
not able to subdivide patients into these more specific groups and
grouped together frontal and occipital lobe patients as extratemporal
and mesial and neocortical temporal lobe patients as temporal. In a larger
sample of well-characterized patients, our results may have resembled
those of Herman and colleagues. Nonetheless, our findings suggest that
seizures during sleep are not limited to those with extratemporal lobe
epilepsy and are common in those with temporal lobe epilepsy.

There are several limitations of our study. First, as EEG coverage was
limited in the sleep laboratory patients, unrecognized seizures may have
occurred. These may have resulted in decreased REM sleep.25 How-
ever, these patients were monitored continuously throughout the night so
that clinical seizures should not have been missed, even with the limited
monitoring used. A related limitation is that some epileptic seizures of
frontal lobe origin may lack EEG correlates. To be certain that only
epileptic seizures were included in our study, we required that events had
ictal EEG correlates. Therefore, it is possible that we may have exclud-
ed seizures that did not have EEG correlates. An additional limitation is
that half of our patients were sleep deprived on half of their monitoring
nights. However, sleep deprivation should not have affected the stage of
sleep which seizures emerged from. Although it is possible that sleep
depression could affect the distribution of stages of sleep, we compen-
sated for this by calculating seizure rates that adjusted for the amount of
time spent in each sleep stage. Finally, it was out of the scope of our
methodology to analyze the relationship of seizures to microstructural
elements of sleep, such as K-complexes, sleep spindles, or the cyclic
alternating pattern.26 These measures, including increases in the cyclic

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alternating pattern rate, have been reported prior to seizure occurrence and may also be important in understanding the relationship of seizures to sleep.

Further clinical and basic science investigation will be needed to understand how different levels of NREM sleep depth influence epileptic seizures and how seizures are related to IEDs. Such study may further our understanding of the pathophysiological processes that facilitate seizures at any given time in an individual with epilepsy and our treatment of this paroxysmal disorder.

ACKNOWLEDGMENTS

We are indebted to Dr. Michael Aldrich for providing comprehensive sleep study reports with precise information pertinent to our manuscript. Ms. Karen Angell assisted with analysis of sleep studies, and Mr. Kevin Weatherwax assisted with figure preparation.

REFERENCES