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Interictal Epileptiform Discharges Do Not Change before Seizures during Sleep

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Summary: *Purpose:* Whether interictal epileptiform discharges (IEDs) increase, decrease, or are unchanged before epileptic seizures has implications for the pathophysiology of epilepsy. Prior studies relating IEDs and seizures have not demonstrated a change in IEDs before seizures. However, they have not controlled for changes in the depth of sleep. Our objective was to test the hypothesis that IEDs are related to seizures during sleep while adjusting for log delta power (LDP), a continuous measure of sleep depth.

Methods: Twenty-two seizures during sleep were identified in 16 subjects with epilepsy admitted for presurgical monitoring. The IEDs that occurred in the hour of sleep before each seizure were used to test the relation between IEDs and seizure occurrence. Sleep depth was measured by LDP (quantity of 1- to 4-Hz activity in 30-s epochs), and records were scored visually for sleep staging and for IEDs. Multivariate logistic regression analyses were applied.

Results: Adjusting for LDP, number of seizures before the current seizure, quartile of the night, and total number of IEDs that occurred during the night, IED did not increase or decrease before seizures ($p > 0.1$). The rate of IEDs increased directly with LDP ($p = 0.0001$), as shown in prior work.

Conclusions: IEDs are not activated or suppressed before seizures during sleep, suggesting that different pathophysiologic processes underlie these two phenomena. These results corroborate prior studies, while providing a more advanced analysis by adjusting for sleep depth and applying multivariate logistic regression analyses. **Key Words:** Epilepsy—Seizure—Interictal epileptiform discharges—Sleep—Statistics.

Focal interictal epileptiform discharges (IEDs), sharp transients in the electroencephalographic (EEG) background between seizures, are the EEG correlates of the depolarization shift (DS) (1). The DS, consisting of a large depolarization of the neuronal membrane associated with a burst of action potentials, has extensively been characterized in terms of underlying basic mechanisms. The relationship of IEDs to epileptic seizures, however, remains unclear. The IEDs may trigger seizures, inhibit them, or be epiphenomena in relation to seizure occurrence. Defining their relation to seizures may be useful in understanding the pathophysiologic processes that may bring on a seizure as well as serving as a predictive indicator for seizure onset.

Most clinical neurophysiologic studies have reported that IEDs do not change significantly in the preictal hour (2–4). Limitations of these studies include (a) presentation of data was mainly descriptive in these studies, with only one study (4) performing a statistical analysis across patients; (b) adjustment for the depth of sleep was not made; and (c) automated IED detection was used. Even when visual analysis is used to confirm IEDs, the possibility still exists that true IEDs may be missed by automated IED detection.

Recently the depth of sleep has been shown to have a direct relation to IED occurrence. Malow et al. (5) studied the relation of spikes to absolute log delta power (LDP), a continuous measure of sleep depth in eight patients with partial epilepsy. Within non–rapid eye movement (NREM) sleep, IEDs were more likely to occur at higher levels of LDP. These findings were later confirmed in another study of 21 patients with medically refractory temporal lobe epilepsy (6). Other independent groups of investigators previously found that IEDs were more common in deeper sleep stages in both surface (7) and intracranial (8,9) recordings. These results suggest that the study of the relation between rate of IED occurrence and seizures during sleep should adjust for sleep depth before making any further conclusions.

To provide a more thorough examination of the relation between IEDs and seizures, we studied patients who had been admitted for presurgical monitoring and who

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had video-EEG polysomnography to identify seizures, IEDs, sleep stages, and to measure the depth of sleep. Using statistical methods that adjusted for repeated measures on patients, the depth of sleep could be included as a factor in the analysis of this relation, and therefore its confounding influence was removed from the study.

METHODS

Subjects and seizures

The records of all adult epilepsy patients admitted for presurgical monitoring at the University of Michigan Epilepsy Laboratory between July 1998 and June 2000 were reviewed to identify seizures that occurred during sleep. Subjects ranged in age from 19 to 53 years (mean ± SD = 39.4 ± 9.7 years) and consisted of nine men and seven women. All had complex partial seizures with or without secondary generalization, and the majority (11 of 16; 69%) had partial seizures of temporal lobe origin. Five subjects had possible extratemporal lobe seizures. The localizations were based on the results of the presurgical evaluation, with a combination of all of the data available, including scalp-EEG recordings, invasive monitoring recordings, brain magnetic resonance imaging (MRI) results, and surgical outcome results. All seizures had both clinical and electrographic manifestations except for six subclinical seizures in four subjects, which had only electrographic manifestations and did not arouse subjects from sleep. Antiepileptic medications (AEDs) were tapered to provoke seizures. Time before seizures ranged from 22 to 60 min (mean ± SD = 47.3 ± 11.3). We did not include subjects with <10 min of sleep before a seizure, fewer than five IEDs in the total night of study, or fewer than two IEDs in the hour before seizures. To facilitate seizures, all subjects were being tapered off AEDs with a uniform protocol, and six subjects also underwent sleep deprivation every other night. All subjects were participating in a research protocol examining the effects of sleep deprivation versus normal sleep on facilitation of seizures, in which they were randomly assigned to sleep deprivation or to normal sleep (10). Data from the six sleep-deprived patients were obtained from nights that they slept.

Video-EEG polysomnography

All subjects underwent continuous digital video-EEG monitoring (Telefactor Corporation, West Conshohocken, PA, U.S.A.) as part of their epilepsy surgery evaluation. The standard 10-20 system (11) was implemented along with sphenoidal electrodes. Electrooculogram (EOG) and chin electromyogram (EMG) channels were included to score sleep stages. The EEG was digitized using 200 Hz, and filter settings were set at 0.3 and 70 Hz. All patients were observed over one night. Subjects were asked to sleep between 10 p.m. and 6 a.m.

Sleep scoring and calculation of log delta power

Each subject's recording was partitioned into display epochs of 30 s each for the purpose of sleep scoring. Visual scoring was performed with a modification of standard criteria (12). Because we did not have access to C3-A2, we used four channels, predominantly C3-O1 and C4-O2 with reference as needed to FP1-C3 and FP2-C4. All records were scored by M.L.M, a registered polysomnographic technologist. NREM stages 3 and 4 were combined into one stage. 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 Fast Fourier Transform (FFT) for 2-s segments. Half-over-lapping 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 s, and LDP was calculated by multiplying the log base 10 of the delta power by a factor of 10. Epochs of wake and artifact, detected by visual inspection, were excluded from the study.

Determination of IEDs

Visual determination of IEDs within 20-s display epochs was performed after sleep staging was completed. The following reformatted montage was used for IED determination: Fp1-F7, F7-T3, T3-T5, T5-O1, Fp2-F8, F8-T4, T4-T6, T6-O2, C3-T3, T3-Sp1, Sp1-Sp2, Sp2-T4, T4-C4, FZ-CZ, CZ-PZ, F7-F3, F3-FZ, FZ-F4, and F4-F8. The inclusion criteria were adapted from those of Gloor (13) and included (a) restricted triangular transient clearly distinguishable from background activity, with the spike component having an amplitude of at least twice that of the preceding 5 s of background activity in any channel of EEG, (b) duration of ≤200 ms, and (c) presence of a field, as defined by involvement of a second adjacent electrode. Our rationale for including an amplitude criterion was to interpret IEDs conservatively and to exclude equivocal IEDs. Two authors (B.A.M. and M.L.M) independently performed visual detection on one NREM–REM cycle within each subject's recording. In studies in which IEDs were detected by one author and not by another, the IEDs in question were reviewed, and a consensus reached about which events constituted IEDs. The remainder of the study was then reviewed for IEDs by B.A.M., who was blinded to the time when the seizure occurred. Data were analyzed to determine the relation of IEDs to seizures while adjusting for LDP. Many of our subjects had either unilateral IEDs or a small number of independent, bilateral IEDs. Therefore, to maximize our sample size, and therefore statistical power, we did not separate the various categories of IEDs (e.g., left temporal, right temporal).

Statistical analyses

The same 30-s epochs created for sleep scoring and LDP measurement were used for analysis. In only 5% of the data did instances occur of more than one IED within a single epoch. Therefore, it was determined that a binary indicator for IED occurrence (1, IED occurred; or 0, IED not occurred) in each 30-s epoch would be more suitable for analysis rather than a more complex indicator for multiple IEDs. For each subject, the quartile of the night that the seizure occurred (calculated from sleep onset to time of waking), the number of prior seizures that night, and the total number of IEDs the subject had during the night were determined.

These factors were included in the model to account for biologic differences between patients, and to adjust for their confounding influence on the occurrence of IEDs. Quartile of the night that the seizure occurred was included in the analysis to adjust for the domination of certain stages of sleep during the night, because these stages in and of themselves have relations to IED occurrence. Number of prior seizures was also included because prior seizure occurrence during the night could be correlated with subsequent seizures and thus have an effect on the occurrence of IEDs. Finally, the total number of IEDs that occurred during the night was considered because subjects had variable numbers of IEDs. Thus a subject who had 10 IEDs the hour before the seizure and had 20 total IEDs for the entire night would contribute different information to the analysis from that of a subject who also had 10 IEDs the hour before the seizure but had 100 total IEDs for the entire night. The former would imply increasing IEDs before the seizure, whereas the latter would imply that IEDs occurs evenly over the night regardless of when the seizure occurs.

All analyses were performed with the SAS statistical package (SAS Institute Inc, Carey, NC, U.S.A.). The study involved taking repeated measurements (e.g., IEDs and LDP) on the same subject over time. Such a design introduces correlations between observations within a cluster of observations from the same subject. If the analysis did not adjust for these correlations, our results would underestimate the standard error and would be more likely to give us falsely significant results. To analyze these data properly, a logistic regression was performed based on generalized estimating equations (GEEs) (14). The log odds of having an IED [log(probability of having an IED/probability of not having an IED)] was modeled as a function of LDP, time, total number of IEDs in the night, quartile of the night of seizure occurrence, and the number of prior seizures. The method of GEEs requires a correlation matrix to be specified that explains the type of relation between IEDs within each seizure. In our analysis, an exchangeable correlation matrix was specified, which assumes that IEDs are equally correlated among each other within a seizure regardless of how close or far apart they are from each other. We explored other correlation matrices, and they showed similar results.

Stage of sleep presented another confounding influence on the occurrence of IEDs. Therefore this analysis was applied to all data as well as to two subsets of the data. One subset included only those observations that occurred during NREM sleep, excluding rapid eye movement (REM) sleep. The other subset consisted of 15 seizures, in 11 subjects, in which the hour before consisted of continuous NREM sleep. Stage of sleep was considered as a factor in this analysis because past studies have shown that NREM sleep activates IEDs, whereas REM sleep suppresses IEDs (15). Therefore, epochs of REM sleep would provide little information for analysis of IED occurrence because there is minimal IED activity in these periods. To account for differences in IED activity between REM and NREM sleep, the GEE model was applied to the two subsets of data to see whether the results still held during NREM sleep epochs.

We determined whether differences in gender, age, seizure type (e.g., partial vs. secondarily generalized), and sleep deprivation affected the relation between IEDs and seizures by using the χ^2 test for categorical variables and an independent samples *t* test for continuous variables. For all statistical tests, the level of significance was set at $\alpha = 0.05$.

RESULTS

Twenty-two seizures occurred in 16 subjects. Seven seizures occurred in quartile 1, four in quartile 2, three in quartile 3, and eight in quartile 4. Of the 22 seizures studied, 13 occurred in subjects who had no prior seizures during the study, four occurred in subjects who had one prior seizure, three occurred in subjects who had two prior seizures, and two occurred in subjects who had three prior seizures. Total number of IEDs ranged from 9 to 1,697 (mean ± SD = 234 ± 419.5). Number of IEDs in the preictal period ranged from 2 to 115 (mean ± SD = 27.1 ± 27.7). Only two subjects had preictal periods containing two IEDs. Nineteen of 22 seizures were partial complex seizures, and three seizures were secondarily generalized. These three seizures occurred in three subjects. Fourteen seizures occurred in the temporal lobe, and eight seizures, occurring in five subjects, had possible extratemporal origins. Finally, six of 16 subjects were sleep deprived; these six subjects contributed 10 seizures (occurring during sleep on non–sleep-deprived nights) to the study.

The GEE model, using all of the data and adjusting for prior seizures, quartile of the night, and total number of IEDs, found no relation between seizure and IED occurrence ($p > 0.01$). LDP, however, was associated with a higher probability of IED occurrence ($p = 0.03$) as

shown in previous work (5,6). The parameter estimate for LDP indicates that for a 5-unit microvolt increase in LDP, the odds of having an IED is 1.5 times as likely. The analysis also showed that studies having a higher total number of IEDs were associated with a higher chance of IED occurrence ($p = 0.0001$). No other factors in the model were related to IED occurrence. Figure 1A and B illustrate the relation of IEDs to seizures in two separate subjects.

Similar results were seen using the subset of data limited to epochs occurring during NREM sleep, excluding REM sleep epochs. No relation was found between IED occurrence and seizures ($p > 0.01$). The GEE analysis showed that LDP had a significant relation to IED occurrence ($p < 0.0001$). The coefficient of LDP indicated that for a 5-microvolt increase in LDP, there was a 2.2 times increase in the probability of IED occurrence. Also concurring with these results, total number of IEDs was significantly related to seizure occurrence ($p < 0.0001$).

Finally, the subset of 15 seizures in 11 subjects with continuous NREM sleep with no wakefulness for the entire hour before the seizure was used to carry out the GEE model. Similar results were found. Seizures were not significantly related to IED occurrence ($p > 0.01$), whereas LDP and total number of IEDs were significantly related to IED occurrence ($p = 0.01$ and 0.02, respectively). The analysis showed that the odds of IED occurrence increased by 2.0 times with a 5-microvolt

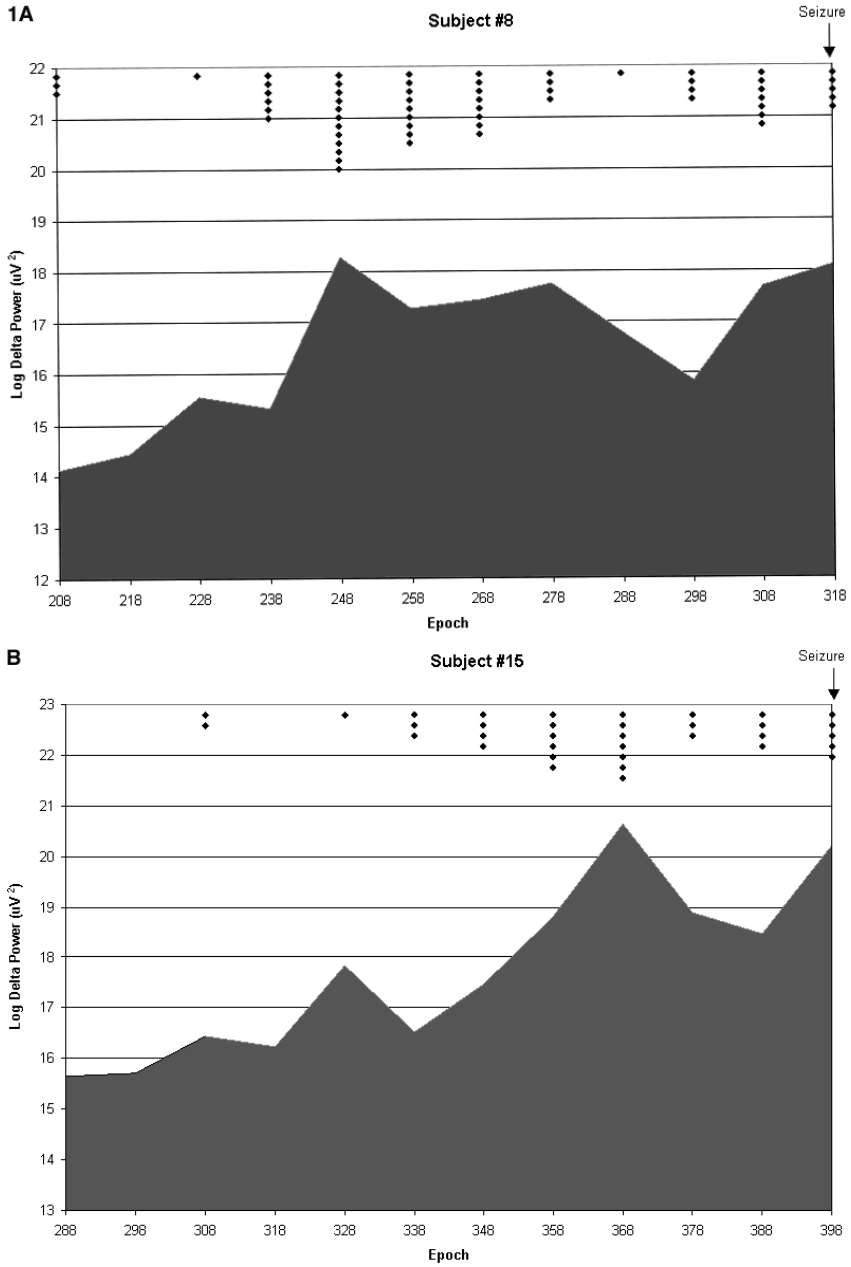

FIG. 1. Relation of epileptiform discharges (IEDs) to log delta power (LDP) during sleep in two subjects **(A, B).** Each diamond represents one IED. Each point on the graph represents the average LDP over a 5-min period. Graphs encompass the hour of sleep before a seizure. Spikes clearly increase with LDP, but do not increase or decrease as the seizure event nears.

increase in LDP. Total number of IEDs also was significantly related to seizure occurrence ($p < 0.0001$).

Age, gender, seizure type (partial vs. generalized), seizure localization (temporal vs. extratemporal), and sleep deprivation did not influence our results. The GEE models were applied to subsets of seizures: complex partial seizures, seizures occurring in sleep-deprived patients, and possible extratemporal seizures. All analyses concurred with our overall results; however, the subset involving possible extratemporal seizures was too small to estimate the GEE parameters correctly, and therefore results could not be confirmed in this subset.

Further analyses were performed to test the hypotheses that (a) seizures are related to IEDs even when LDP is excluded from the model, and (b) seizures are related to LDP. GEE models excluding LDP still showed no relation between seizures and IEDs. A linear mixed model showed no relation between LDP and seizures.

DISCUSSION

Our data showed no change in the probability of IED occurrence in the period before seizures during sleep, even after accounting for LDP. Our findings also showed that the probability of IED occurrence increased as LDP increased. An increased number of total IEDs also led to significant increases in the probability of IED occurrence.

To analyze these data and types of variables, we used a logistic regression model based on the method of GEEs to look for a relation between IED occurrence and seizures. Such a method enables us to analyze continuous data, and it also is robust to missing data (i.e., as occurred in those epochs with wake or artifact). Because the data involve measurements from the same subject, correlations between observations also can be handled by a GEE model. Our analysis therefore, provides a more thorough approach to answering the question of whether seizures are related to IED occurrence. Our analysis adjusts for differences in sleep depth, which have been shown to have a significant impact on the probability of IED occurrence. We also looked at differences in IEDs across a continuum of time and not in predefined intervals. Quartile of the night, prior seizures, and total number of IEDs during the night also were accounted for.

These observations are consistent with earlier findings of no change in the rate of IEDs before seizures (2–4). These important studies laid the foundation for the work presented here. Our data provide confirmation of these studies by using statistical analyses that adjust for sleep depth and other variables, and by using visual IED confirmation as opposed to automated IED detection with visual confirmation. Although the automated approach with visual confirmation eliminates false-positive IEDs, it may miss true-positive IEDs not detected by the automatic IED program. We also were able to control for state of arousal by using LDP, a continuous measure of sleep depth. Use of continuous measure of the depth of sleep is advantageous over use of categorical states of arousal (e.g., NREM stages 1, 2, 3, 4, and stage REM), which result in loss of information.

Our data do not support that IEDs facilitate or inhibit seizures during sleep. The lack of a temporal relation between IEDs and seizures is intriguing, as both events are activated by NREM sleep and suppressed by REM sleep (15). However, whereas IEDs are activated by increases in sleep depth (6), seizures appear to be more common in lighter sleep stages (16–18). Additionally, we did not find a relation between LDP and seizures. This discrepancy suggests that different pathophysiologic processes underlie the two phenomena. Steriade et al. (19) postulated that progressive hyperpolarization within thalamocortical projection neurons predisposes to epileptic activity during sleep. The IEDs and seizures may be preferentially activated by different levels of hyperpolarization within these thalamocortical projection neurons. An alternative explanation is that epileptic seizures may be facilitated by sleep-state transitions, which result in changes in the levels of hyperpolarization within thalamocortical projection neurons. This model may explain why pathophysiologic processes such as obstructive sleep apnea, which fragment sleep, have been associated with worsening seizure control, and why treatment of these disorders may improve seizure control (20–22).

One of the limitations of our study is that we used surface EEG recordings. As compared with intracranial recordings, surface EEGs may miss interictal activity and also may contain more artifacts. Because many of our subjects had either unilateral IEDs or a small number of independent, bilateral IEDs, we were not able to separate out various categories of IEDs (e.g., left temporal, right temporal). Follow-up studies with larger numbers of patients and intracranial recordings may be useful in studying whether the focality of IEDs preceding a seizure is influenced by seizure onset.

In conclusion, our findings support those of other studies that have reported no change in the rate of interictal spiking before seizures. Our analysis also supports previous work showing that deeper levels of sleep are associated with increased IED occurrence. Further experimental and clinical studies will be needed to unravel the pathophysiologic relation of IEDs to seizures.

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REFERENCES

1. McNamara JO. Cellular and molecular basis of epilepsy. *J Neurosci* 1994;14:3413–25.

2. Lieb JP, Woods SC, Siccardi A, et al. Quantitative analysis of depth spiking in relation to seizure foci in patients with temporal lobe epilepsy. *EEG Clin Neurophysiol* 1978;44:641–3.
3. Gotman J, Koffler D. Interictal spiking increases after seizures but does not after decrease in medication. *EEG Clin Neurophysiol* 1989;72:7–15.
4. Katz A, Marks DA, McCarthy G, et al. Does interictal spiking change prior to seizures? *EEG Clin Neurophysiol* 1991;79:153–6.
5. Malow BA, Kushwaha R, Lin X, et al. Relationship of interictal epileptiform discharges to sleep depth in partial epilepsy. *EEG Clin Neurophysiol* 1997;102:20–6.
6. Malow BA, Lin X, Kushwaha R, et al. Interictal spiking increases with sleep depth in temporal lobe epilepsy. *Epilepsia* 1998;39: 1309–16.
7. Sammaritano M, Gigli GL, Gotman J. Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology* 1991;41:290–7.
8. Rossi G, Colicchio G, Pola P. Interictal epileptic activity during sleep: a stereo-EEG study in patients with partial epilepsy. *EEG Clin Neurophysiol* 1984;58:97–106.
9. Lieb J, Joseph J, Engel J Jr, et al. Sleep state and seizure foci related to depth spike activity in patients with temporal lobe epilepsy. *EEG Clin Neurophysiol* 1980;49:538–57.
10. Malow BA, Passaro EA, Hall JM, et al. Sleep deprivation does not increase seizure frequency during long term monitoring. *Epilepsia* 1999;40:99–100.
11. Jasper H. The 10-20 electrode system of the International Federation. *EEG Clin Neurophysiol* 1958;10:370–5.
12. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects.* Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
13. Gloor P. Contributions of electroencephalography and electrocorticography in the neurosurgical treatment of the epilepsies. *Adv Neurol* 1975;8:59–105.
14. Diggle P, Liang K, Zeger S. *Analysis of longitudinal data.* Oxford: Oxford University Press, 1994.
15. Malow BA. Sleep and epilepsy. In: Aldrich M, ed. *Neurologic clinics: sleep disorders II.* Philadelphia: Saunders, 1996:765–89.
16. Bazil CW, Walczak TS. Effect of sleep and sleep stage on epileptic and nonepileptic seizures. *Epilepsia* 1997;38:56–62.
17. Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep-wake cycle: differences by seizure onset site. *Neurology* 2001;56:1453–9.
18. Minecan D, Marzec M, Malow BA. Seizure rate variability in different stages of sleep. *Epilepsia* 2000;41:167–8.
19. Steriade M, Conteras D, Amzica F. Synchronized sleep oscillations and their paroxysmal developments. *Trends Neurosci* 1994;17: 199–208.
20. Devinsky O, Ehrenberg B, Barthlen GM, et al. Epilepsy and sleep apnea syndrome. *Neurology* 1994;44:2060–4.
21. Vaughn BV, D'Cruz OF, Beach R, et al. Improvement of epileptic seizure control with treatment of obstructive sleep apnoea. *Seizure* 1996;5:73–8.
22. Malow BA, Fromes GA, Aldrich MS. Usefulness of polysomnography in epilepsy patients. *Neurology* 1997;48:1389–94.