Epilepsia, **39**(12):1309–1316, 1998
Lippincott Williams & Wilkins, Philadelphia

Interictal Spiking Increases with Sleep Depth in Temporal Lobe Epilepsy

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Summary: *Purpose:* To test the hypothesis that deepening sleep activates focal interictal epileptiform discharges (IEDs), we performed EEG–polysomnography in 21 subjects with medically refractory temporal lobe epilepsy.

Methods: At the time of study, subjects were seizure-free for ≥24 h and were taking stable doses of antiepileptic medications (AEDs). Sleep depth was measured by log delta power (LDP). Visual sleep scoring and visual detection of IEDs also were performed. Logistic-regression analyses of IED occurrence in relation to LDP were carried out for two groups of subjects, nine with frequent IEDs (group 1) and 12 with rare IEDs (group 2).

Results: The LDP differentiated visually scored non–rapid eye movement (NREM) sleep stages ($p = 0.0001$). The IEDs were most frequent in NREM stages 3/4 and least frequent in REM sleep. Within NREM sleep, in both groups, IEDs were more frequent at higher levels of LDP ($p < 0.05$). In group 1, after accounting for the level of LDP, IEDs were more frequent (a) on the ascending limb of LDP and with more rapid increases in LDP ($p = 0.007$), (b) in NREM than in REM sleep ($p = 0.002$), and (c) closer to sleep onset ($p < 0.0001$). Fewer than 1% of IEDs occurred within 10 s of an EEG arousal.

Conclusions: Processes underlying the deepening of NREM sleep, including progressive hyperpolarization in thalamocortical projection neurons, may contribute to IED activation in partial epilepsy. Time from sleep onset and NREM versus REM sleep also influence IED occurrence. **Key Words:** Sleep—Epilepsy—Electroencephalography—Quantitative EEG—Interictal epileptiform discharges.

Non–rapid-eye-movement (NREM) sleep activates interictal epileptiform discharges (IEDs) in both partial and generalized epilepsy syndromes (1–4). In contrast, rapid-eye-movement (REM) sleep suppresses epileptiform discharges. Experimental models also demonstrated that epileptic foci are modulated by sleep (5,6). The activating role of NREM sleep on epileptic cortex has been attributed to increased neuronal synchronization within thalamocortical projection neurons (7).

The depth of NREM sleep may affect epileptic activity. Several visually scored studies of surface or intracranial recordings in subjects with partial epilepsy demonstrated that delta NREM sleep (stages 3 and 4) activates IEDs preferentially compared with stages 1 and 2 (8–10). By using log delta power (LDP), computed by the Fast Fourier Transform (FFT) as a continuous measure of sleep depth, Malow et al. (11) demonstrated a relation between the level of sleep depth and IED occurrence in eight subjects with partial epilepsy. Within NREM sleep, IEDs were more likely to occur: (a) at higher levels of LDP; (b) on the ascending limb of LDP; and (c) with more rapid increases in LDP. The IED frequency per minute was 4.6 times higher in NREM than in REM sleep and diminished with time from sleep onset. These results suggested that focal IEDs were activated by deepening sleep. To extend these preliminary findings, we analyzed the relation of IEDs to sleep depth in 21 additional subjects recruited from a group of patients undergoing evaluation for epilepsy surgery. These subjects (a) all had medically refractory complex partial seizures of temporal lobe origin with or without secondary generalization; (b) had a variety of pathologic lesions, including mesial temporal sclerosis, gliomas, and cavernous angiomas, and (c) varied widely in the number of IEDs recorded.

SUBJECTS AND METHODS

Subjects

Between December 1995 and February 1997, all subjects undergoing presurgical evaluation in the University of Michigan Epilepsy Laboratory and meeting criteria were asked to participate in the study, and 57% agreed,

Accepted July 20, 1998.
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resulting in 21 subjects (Table 1). Informed consent was obtained, and the studies were carried out under a protocol approved by the University of Michigan Institutional Review Board. Participants met the following criteria: age, 18–65 years; ability to give informed consent; a history of recent recurrent unprovoked focal seizures with at least one seizure in the preceding 3 months; ictal semiology and recordings consistent with complex partial seizures of temporal lobe origin (12); no evidence of psychogenic seizures; and no recent medication discontinuation. We restricted our sample to those who had undergone ictal recordings to ensure that the diagnosis of partial epilepsy was accurate. No subjects had extratemporal lesions on brain magnetic resonance imaging (MRI) except for subject 5, who had a left temporal glioma involving primarily mesial temporal structures with additional involvement of the inferior frontal lobe, and subject 11, who had right hemispheric encephalomalacia predominantly involving the right lateral temporal lobe. In six subjects with normal brain MRIs, seizures were localized to the temporal region by either scalp or intracranial monitoring, and ictal semiology was consistent with temporal lobe epilepsy (12).

EEG–polysomnography

All subjects underwent continuous video-EEG–polysomnography with digital EEG (Telefactor Corporation, West Conshohocken, RA, U.S.A.) in the General Clinical Research Center of the University of Michigan Medical Center between April 1996 and April 1997. Subjects underwent two consecutive nights of study with 21 channels of electroencephalography (EEG) and additional channels of electrooculogram (EOG) and chin electromyogram (EMG). The standard 10-20 system was used; additionally, T_1 and T_2 electrodes were applied. The EEG was digitized at 200 Hz, and filter settings were 0.3 Hz (low-frequency filter) and 70 Hz (high-frequency filter). Subjects were seizure free $\geq$24 h before study, most for at least a week, and were receiving stable doses of medication. Antiepileptic drug (AED) trough levels were obtained in the morning after night 1. Levels were therapeutic in all subjects except three with phenytoin (PHT) levels in the 5–10 mg/L range; one of these subjects was also taking sodium valproate (VPA) with a level of 44 mg/L (subject 20), and two of these subjects were taking gabapentin (GBP) with no levels measured (subjects 6 and 17). Because a first-night effect may occur during the initial night of study in a laboratory, resulting in a longer sleep latency and REM latency and an increase in the percentage of wakefulness and stage 1 sleep (13), night 2 was used for the determination of interictal spike occurrence in 15 subjects. In four subjects, complex partial seizures occurred after night 1 and before or during night 2 (subjects 6, 7, 11, and 21) and, as IED rates may increase after seizures (14,15), the first night of study was used for analysis instead. In two additional subjects, electrode artifacts or loss of data interfered with interpretation of night 2, and night 1 was used for analysis (subjects 14 and 20). Preliminary analysis comparing night 1 and night 2 in four subjects, in whom both nights were free of seizures and electrode artifacts,

TABLE 1. *Patient characteristics*

No.	Age/Sex	Yrs of seizures	Seizure freq/mo	Sz during sleep	AED dose/day (mg)	Brain MRI	GTCS	No. of sleep IEDs	REM IEDs	Bilat. IEDs
1	48/F	9	4	Yes	PHT 300	Hippocampal atrophy	No	839	No	Yes
2	54/F	41	12	Yes	PHT 400, LTG 150	Hippocampal atrophy	No	666	Yes	No
3	32/M	25	20	No	CBZ 1600	MTS	Yes	659	Yes	No
4	18/M	13	12	Yes	CBZ 700, LTG 750	MTS	No	527	Yes	Yes
5	52/M	22	12	No	PHT 530, PB 90	Glioma (MT and IF)	No	297	Yes	No
6	38/M	20	2	Yes	PHT 400, GBP 1800	Cavernous angioma (LT)	No	238	Yes	No
7	20/F	15	4	Yes	CBZ 1200	Glioma (MT)	Yes	94	No	Yes
8	20/M	17	4	No	PHT 300, LTG 550	Normal	Yes	76	Yes	No
9	35/M	15	10	Yes	PHT 550	Normal	No	63	Yes	Yes
10	44/F	6	4	Yes	VPA 1250, LTG 200	Hippocampal atrophy	No	33	No	Yes
11	24/M	6	16	No	PHT 300, LTG 50	Encephalomalacia	Yes	25	No	Yes
12	27/F	8	6	No	CBZ 1000, GBP 1200	MTS	No	26	No	Yes
13	47/M	20	4	No	PHT 400, LTG 600	Normal	Yes	23	No	No
14	39/F	5	4	Yes	CBZ 900, LTG 200	Normal	Yes	16	No	Yes
15	39/F	15	4	No	CBZ 1200	Normal	No	18	No	Yes
16	38/F	12	12	Yes	PHT 700	Temporal atrophy	Yes	15	No	No
17	34/F	21	12	Yes	PHT 200, GBP 2700	Temporal atrophy	Yes	13	No	No
18	21/F	16	12	No	OCBZ 2000	MTS	No	8	No	Yes
19	50/F	49	5	No	CBZ 1600	Temporal atrophy	No	5	No	No
20	45/M	21	4	Yes	PHT 400 VPA 2000	Normal	No	4	No	No
21	25/M	24	8	Yes	CBZ 2200	MTS	Yes	2	No	No

Sz, seizures; AED, antiepileptic drug; PHT, phenytoin; LTG, lamotrigine; CBZ, carbamazepine; PB, phenobarbital; GBP, gabapentin; VPA, valproic acid; OCBZ, oxcarbamazepine. MRI, magnetic resonance imaging; MT, mesial temporal; IF, inferior frontal; LT, lateral temporal; MTS, mesial temporal sclerosis; GTCS, generalized tonic–clonic seizures; IEDs, interictal epileptiform discharges; REM, rapid eye movement; Bilat, bilateral.

showed that the overall pattern of IEDs to LDP was comparable for both nights.

Sleep scoring and spectral analysis

Each subject's recording was partitioned into 30-s epochs for sleep scoring. Visual sleep scoring was performed by using standard criteria (16) on channel C_3-A_2 at 10 mm/s. Non-REM stages 3 and 4 were combined into one stage (3/4). An FFT, performed during the recording process by using commercially available software (Telefactor Corporation, West Conshohocken, PA, U.S.A.), was calculated on 2-s segments with a 1-s overlapping window. The central–occipital channel contralateral to the dominant IED focus or, for subjects with bilateral IEDs, contralateral to the side of greater temporal slowing (C_4-O_2 for left temporal IED focus or left temporal slowing and C_3-O_1 for right temporal IED focus or right temporal slowing) was used for analysis. The rationale for performing the FFT on these channels rather than C_3-A_2, the standard channel for sleep staging, was to minimize the effect of pathologic delta activity from the epileptic focus on the FFT calculation. 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 FTT for two second segments. Half-overlapping windows were applied. The frequency resolution was 0.39 Hz, and delta power was calculated by summing the power in the delta frequency range, between the 0.79 bin and the 3.9 Hz bin. Delta power (μV^2) was averaged over 30 s, and LDP was calculated by multiplying the log (base 10) of the delta power by a factor of 10. The FFT results and the visually scored sleep stage for each 30-s epoch within each subjects' study were entered into a spreadsheet. Awake epochs and epochs containing myogenic artifact were excluded from the analysis. The EEG background 10 s before and 10 s after each IED were reviewed to determine the presence or absence of an arousal, defined by American Sleep Disorders Association criteria as a shift of frequency to the alpha or theta range for $\geq$3 s (17).

Determination of IEDs

Determination of IEDs was performed after sleep staging had been completed. The following reformatted montage (Telefactor Digital EEG System; 15-s epochs; 20 mm/s) was used for IED determination: C_3-T_3, T_3-T_1, T_1-T_2, T_2-T_4, T_4-C_4, Fp_1-F_7, F_7-T_3, T_3-T_5, T_5-O_1, Fp_2-F_8, F_8-T_4, T_4-T_6, T_6-O_2, F_7-E_z, T_1-E_z, T_3-E_z, F_8-E_z, T_2-E_z, T_4-E_z (E_z is placed halfway between C_z and P_z). The inclusion criteria for IEDs were adapted from those of Gloor (18) 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 $\leq$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 spikes. Rare spikes appeared in clusters and were counted as individual events. Benign epileptiform transients of sleep and wicket spikes were excluded, as were physiologic sleep transients, including vertex waves. Two of the authors (B. A. M. and M. S. A.) 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 the first author (B. A. M.). The IED data were combined with sleep stages by using a software program that one of the authors (R. K.) developed to interface with the Telefactor system. Data were analyzed to determine the relation of IEDs to NREM and REM sleep and to sleep depth, as measured by LDP.

Statistical analyses

The 21 subjects consisted of nine patients with relatively frequent IEDs (range, 63–839 IEDs per night; group 1) and 12 patients with relatively rare IEDs (range, 2–33 IEDs per night; group 2). Groups 1 and 2 were analyzed separately because of several differences between these groups. First, preliminary analysis showed that the groups differed in the linearity of LDP–IED relation; the LDP to IED relation was linear in group 2 and nonlinear in group 1. Second, because no IEDs occurred during REM sleep in group 2, the effect of NREM/REM sleep on IED occurrence could not be studied in these subjects. Finally, because the number of IEDs in group 2 was relatively small, there was not enough variability in spiking among epochs containing IEDs to study the direct relation between the number of IEDs and the LDP within a 30-s epoch. Therefore, a binary indicator for IEDs (1 = IED, 0 = no IED) was created for the group 2 subjects. In contrast, in group 1, the number of IEDs was relatively large, and a categoric indicator for IEDs (category 3 = 11 or more IEDs; category 2 = 6–10 IEDs; category 1 = 1–5 IEDs; category 0 = no IEDs) within a 5-min epoch was created. Five-minute epochs were used instead of 30-s epochs because of the excessive computing requirements needed for characterizing the relation between a categoric indicator for IEDs and LDP throughout the night. Compared with group 2, group 1 provides more information regarding the effects of LDP and REM sleep on the occurrence of IEDs.

For each subject, LDP, LDP slope, and normalized LDP were determined. For group 1, the 30-s epochs of LDP resulting from the FFT calculation were averaged over 5-min epochs. Slope of LDP for 5-min epochs [(average LDP in 5-min epoch – average LDP in the pre-

ceding 5-min epoch)/5 min] also was calculated. Normalized LDP (average LDP in 5-min NREM epoch – average LDP for REM epochs in that subject) was determined for each NREM epoch. For group 2, 30-s epoch values were used for LDP, the slope of LDP [(LDP in 30-s epoch – LDP in the immediately preceding 30-s epoch)/30 s], and the normalized LDP (average LDP in 30-s NREM epoch – average LDP for REM epochs in that subject). The measure of LDP was used to assess how well LDP discriminated visually scored sleep stages (mixed model; shown subsequently). The normalized LDP was used for analysis of IED occurrence (generalized estimating equations) as preliminary analysis showed that IED occurrence is more influenced by normalized LDP than by absolute levels of LDP, which vary widely among subjects. The slope of LDP also was used for the analysis of IEDs to study whether IEDs are more likely to occur on the ascending limb of LDP.

Analyses were performed by using the SAS statistical package (SAS Institute Inc., Carey, NC, U.S.A.). This study, which used a longitudinal design, involved multiple observations from the same subject over time that are likely to be correlated (i.e., the occurrence of one IED makes the occurrence of a second IED in that subject's study more likely). To account for the correlations of observations over time measured from the same subjects, we performed multivariate statistical analyses on our data, accounting for repeated measures. The mixed model was applied to determine whether LDP, a normally distributed continuous variable, discriminated visually scored sleep stages and to study the change of LDP over time (19). For group 2, a multivariate analog of logistic regression, based on the generalized estimating equations (GEEs), was used to determine the effect of normalized LDP, slope of LDP, and time from sleep onset on IED occurrence. Note that, because no IEDs occurred for all 12 subjects during REM sleep, we limited our analysis in this group to the observations during NREM sleep. Specfically, we modeled the log odds of having an IED [log (probability of having an IED/probability of not having an IED)] in each 30-s epoch as a function of normalized LDP, slope of LDP, and time from sleep onset. Because the probability of having an IED in any given epoch is very small, the odds and probability are approximately the same. Each of these factors was studied individually and simultaneously to control for the confounding effect of the other variables.

For group 1, because the number of IEDs is classified into several ordered categories, a multivariate analog of proportional odds model using GEEs was used to study the effects of LDP, slope of LDP, time from sleep onset, and NREM/REM sleep on the number of IEDs (20). Specifically, we simultaneously modeled the log odds of having at least one IED vs. no IEDs, the log odds of having six or more IEDs versus five or fewer IEDs, and the log odds of having ≥ 11 IEDs versus ≤ 10 IEDs in each 5-min epoch as functions of normalized LDP, LDP slope, time from sleep onset, and NREM versus REM sleep.

Differences between groups 1 and 2, including age, sex, years of seizures, seizure frequency, presence of sleep-related seizures, number of AEDs, abnormal brain MRI studies, presence of secondarily GTCS, presence of mesial temporal lobe epilepsy (defined by having either mesial temporal lobe lesions or mesial temporal lobe seizure onset by depth electrode monitoring), or presence of unilateral temporal foci were assessed by using Fisher's Exact test for categoric variables and the Student's t test for continuous variables. For all statistical tests, the level of significance was set at $\alpha = 0.05$.

RESULTS

Parameters for visually scored sleep stages

The total recording time, total sleep time, and distribution of visually scored sleep stages are displayed in Table 2. The percentages of NREM stage 1, 2, 3/4, and stage REM were similar to those reported in our preliminary report of the relation of IEDs to sleep depth, in which the percentages of total sleep time were 12% for NREM stage 1, 56% for NREM stage 2, 15% for NREM stages 3/4, and 17% for REM sleep.

Log delta power discriminates visually scored sleep stages

Data from groups 1 and 2 were combined to study how LDP discriminates visually scored sleep stages. Stage REM and NREM stage 1 did not differ significantly in LDP, whereas NREM stages 1, 2, and 3/4 differed significantly in LDP ($p = 0.0001$; Table 3). Controlling for sleep-stage effect on LDP, there was a 0.14 μV^2 decrease in LDP, on average, for every hour of sleep ($p = 0.02$). Nights for two representative subjects, one from group 1 and one from group 2, are illustrated in Fig. 1. We and others previously described the findings of (a) high LDP in the first sleep cycle with a dampening of LDP in subsequent sleep cycles, and (b) low LDP during REM sleep (11,21).

Interictal spike occurrence in relation to normalized LDP, slope of LDP, time, and NREM versus REM sleep

Combining groups 1 and 2, the proportion of epochs containing IEDs was highest in NREM stages 3/4 and

TABLE 2. *Parameters for visually scored sleep stages*

Total recording time, min (mean ± standard deviation)	439 ± 22
Total sleep time, min (mean ± standard deviation)	365 ± 70
NREM stage 1 (% of total sleep time)	15%
NREM stage 2 (% of total sleep time)	56%
NREM stage 3/4 (% of total sleep time)	12%
REM (% of total sleep time)	17%

TABLE 3. *Mean LDP differences among visually scored sleep stages*

Sleep-stage pair	Mean LDP difference	SEM	p Value
NREM 1 vs. REM	0.08	0.07	0.3
NREM 2 vs. NREM 1	4.88	0.06	0.0001
NREM 3/4 vs. NREM 2	4.39	0.07	0.0001

LDP, log delta power; SEM, standard error of mean.

lowest in REM sleep (Table 4). To better define the relation of IEDs to sleep depth, we studied the effects of normalized LDP, slope of LDP, time, and REM versus NREM sleep on IEDs for groups 1 and 2 separately. Although we combined subjects into two groups for the statistical analyses, each individual subject's data were examined in detail. All 21 subjects, regardless of group, showed a direct relation of IEDs to NREM sleep depth. Representative graphs for two subjects, one from group 1 and one from group 2, demonstrated the IED-to-NREM sleep depth relation (Fig. 1).

For group 1, the GEE proportional-odds model analysis, including all of these variables, showed that higher normalized LDP is associated with a higher chance of having more IEDs. For example, the odds of having at least one IED in a given 5-min epoch for a subject with normalized LDP >6.8 μV^2 (75th percentile of LDP) is 3.0 times higher than that for a subject with normalized LDP <0.7 μV^2 (25th percentile of LDP; $p = 0.04$).

For group 1, our results also illustrate that IEDs are more likely to occur on the ascending limb of LDP—as delta power increases—than on the descending limb. Specifically, on the ascending limb, the coefficient of the slope variable suggests that the odds of having one or more IEDs in a given 5-min epoch increases by 1.4 times for each 1 μV^2/5-min increase in slope ($p = 0.007$). The IEDs also are more likely to occur earlier in the night, with the odds of having at least one IED in a 5-min epoch at a given time being 0.88 times less than at 1 h earlier ($p < 0.0001$). Finally, IEDs are more likely to occur during NREM sleep as compared with REM sleep, with the odds of having at least one IED in a 5-min epoch during NREM sleep being 2.4 times higher than that during REM sleep ($p = 0.002$). The estimated effect of each variable presented has accounted for the effects of the other variables. For example, the estimated effect of NREM versus REM sleep had accounted for the effects of normalized LDP, slope of LDP, and time.

For group 1, similar conclusions can be stated for the odds of having six or more IEDs (as compared with having five or fewer IEDs) and the odds of having ≥ 11 IEDs (as compared with having ≤ 10 IEDs) in a given 5-min epoch. For example, the odds of having six or more IEDs in 5 min as compared with having five or fewer IEDs in 5 min is 2.4 times higher during NREM sleep than during REM sleep.

For group 2, higher normalized LDP also was associated with a higher chance of having more IEDs. The GEEs analysis showed that the odds of having an IED in a given 30-s epoch increased by 2.1 times for every 5 μV^2 change in normalized LDP ($p = 0.0002$). In contrast to group 1, the slope of LDP was not predictive of IEDs ($p = 0.71$), and time from sleep onset also was not significant ($p = 0.49$). These differences between subject groups may be related to the greater number of IED observations in group 2 (see Discussion). Because no subjects in group 2 had IEDs during REM, the NREM versus REM effect on IEDs could not be assessed in this group.

Structure and lateralization of IEDs

The IED structure varied widely in NREM sleep, with marked fluctuations in the sharpness and amplitude of IEDs recorded even within the same 30-s epoch. Within REM sleep, spikes were more uniform and tended to be lower in amplitude in REM sleep, as observed by previous investigators (8,22).

As Table 1 shows, 10 subjects had bilateral IED foci recorded during overnight sleep recordings. In two subjects (4 and 15), IEDs were bilateral on routine EEGs and remained bilateral during overnight sleep. Overnight recordings activated additional IED foci not present on routine EEGs in eight subjects as follows. In two subjects (7 and 11) with unilateral IED foci on routine EEGs, an additional contralateral IED focus was activated by NREM stages 2 or 3/4. In six subjects with no IEDs on routine EEGs, three subjects (1, 9, and 14) had bilateral IED foci activated by stage 1 sleep, two subjects (12 and 18) had unilateral IED foci activated by stage 1 sleep with stage 2 or 3/4 sleep needed to activate bilateral IED foci, and one subject (10) had no IED foci in stage 1 sleep and bilateral IED foci in stage 2 sleep. In only one case were bilateral IED foci recorded during REM sleep; this subject (4) had bilateral IEDs recorded on routine EEG. Four additional subjects (16, 17, 19, and 21) had no IEDs recorded on routine EEGs and unilateral IEDs recorded on overnight sleep recordings. Routine EEGs contained wakefulness and stage 1 sleep in all cases and stage 2 sleep in some cases. None contained stage 3/4 sleep or REM sleep.

Occurrence of IEDs in relation to arousals

Fewer than 1% of IEDs were preceded or followed within 10 s by arousals, defined by American Sleep Disorders Association criteria as a shift of frequency to the alpha or theta range for ≥ 3 s (17).

Differences between groups 1 and 2

Groups 1 and 2, defined by the number of IEDs, did not differ in age, sex, years of seizures, seizure frequency, presence of sleep-related seizures, number of AEDs, abnormal brain MRI studies, presence of second-

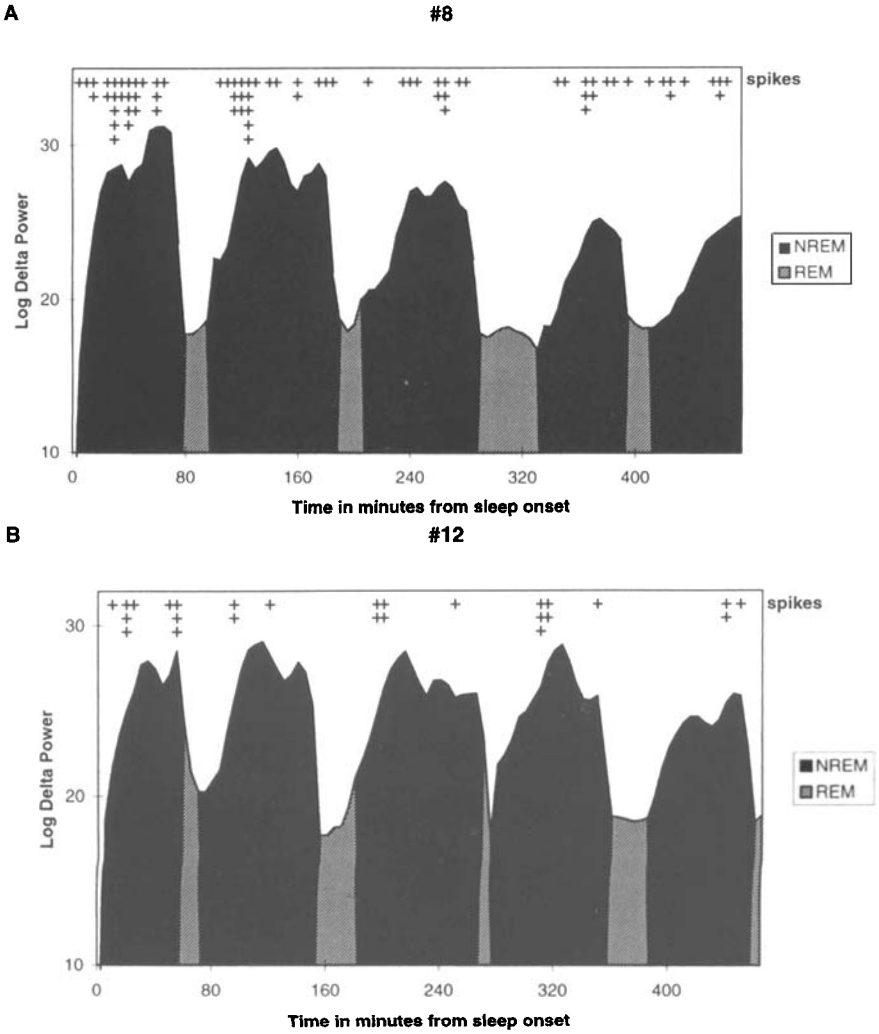

FIG. 1. A, B: Relation of interictal epileptiform discharges (IEDs) to LDP (μV^2) in two subjects, one from group 1 (no. 8) and one from group 2 (no. 12). Each + symbol represents one IED. The LDP during NREM sleep is illustrated in black; LDP during REM sleep is illustrated in gray. Each point on the graph represents a moving average of three consecutive blocks, with each block representing an average of 10 consecutive epochs. To avoid averaging REM and NREM sleep epochs, the first and last block of each NREM and REM sleep cycle were not averaged. Note that spikes cluster on the ascending limb of maximal delta power.

arily GTCS, presence of mesial temporal lobe epilepsy, or presence of unilateral temporal foci ($p > 0.1$). The only significant difference between the two groups, apart from IED number, was the higher prevalence of REM IEDs in group 1 ($p = 0.0003$). Seven of nine subjects in group 1 had REM IEDs as compared with no subjects in group 2 with REM IEDs.

DISCUSSION

In this study, we confirmed and extended earlier preliminary findings of a direct relation between NREM sleep depth and IED occurrence in partial epilepsy. Our 21 subjects were recruited from a group of medically refractory subjects with temporal lobe epilepsy. All subjects showed a direct relation of IED occurrence to normalized LDP, despite heterogeneity in IED frequency and brain MRI pathology. Those with normal MRIs, structural lesions, or hippocampal atrophy or sclerosis demonstrated similar patterns of IED activation by increased levels of LDP. Rapid-eye-movement sleep activated IEDs in seven subjects, with relatively frequent IEDs throughout the night being the only significant predictor of REM IED occurrence.

After accounting for LDP effects, group 1 (frequent-IED group) subjects also demonstrated an activating effect of NREM sleep (vs. REM sleep) on IEDs, a direct relation between LDP slope and IEDs, and an inverse relation between time from sleep onset and IEDs. Because we accounted for LDP effects, the increased likelihood of IEDs closer to sleep onset and in NREM sleep cannot be attributed to higher LDP at these times. The effect of REM sleep on IEDs could not be assessed in

TABLE 4. *Proportion of IEDs among visually scored sleep stages*

Sleep stage	IEDs	Total no. of min	Avg no. of IEDs/min
REM	179	1327.5	0.135
NREM 1	393	1,118.5	0.331
NREM 2	2,193	4,284	0.512
NREM 3/4	882	883.5	0.998
Total	3,647	7,683.5	—

IED, interictal epileptiform discharges.

group 2 (rare-IED group) because all of these subjects lacked IEDs during REM sleep. The effects of LDP slope and time reached statistical significance in group 1 but not in group 2. These findings most likely reflect increased statistical power to detect the independent effects of time and REM versus NREM sleep, given the larger number of observations (IEDs) in group 1 compared with group 2. An alternative explanation is that the relation of IEDs to sleep in subjects with a relatively small number of IEDs differs biologically from those with a relatively large number of IEDs, although clinical differences between groups 1 and 2 were not found. Of note, our preliminary findings in eight subjects with relatively small numbers of IEDs, were similar to our findings in group 2. In those eight subjects, LDP slope was of borderline significance ($p = 0.06$) in predicting IEDs, and the effects of time and REM sleep were not significant after accounting for LDP.

A minority of IEDs (<1%) were preceded or followed by an arousal from sleep. Sleep in temporal lobe epilepsy has been characterized by marked instability with a significant increase in the number and the duration of awakenings and sleep shifts (23). Some authors postulated that this instability may facilitate epileptic activity, including IEDs (24). In contrast, other investigators implied that neurochemical processes underlying the facilitation of NREM sleep, including progressive hyperpolarization in thalamocortical projection neurons, induce a state of relative neuronal synchronization, which facilitates IEDs and epileptic seizures (25). Our results would suggest that processes associated with the deepening of NREM sleep are more important in activating IEDs in temporal lobe epilepsy than are processes associated with arousal from sleep. In most subjects with partial epilepsy, seizures are also more common during NREM sleep than during REM sleep (3,26), although the influence of deepening NREM sleep on seizures is unknown. Further work is necessary to define the influence of deepening NREM sleep on seizures and to determine whether IEDs and seizures are activated by similar pathophysiologic mechanisms.

Our findings are concordant with those of other investigators who examined the relation of IEDs to sleep in partial epilepsy. By using visual scoring methods, Sammaritano et al. (8) found that 31 of 40 subjects with temporal lobe epilepsy had increases in IED frequency during stages 3 and 4 NREM sleep as compared with light NREM sleep, REM sleep, and wakefulness. Intracranial electrode studies of partial epilepsy also demonstrated that, in the majority of subjects, deep NREM sleep preferentially activated IEDs (9,10). We believe that the use of LDP adds additional information to the relation of epileptic discharges to sleep, in that sleep depth is measured continuously, rather than segmented into discrete visually scored sleep stages. The treatment of sleep depth as a continuous variable is congruent with the neurophysiology of the transition from wakefulness or REM to light NREM sleep (NREM stages 1 and 2) and to delta NREM sleep (NREM stages 3 and 4) (27).

Overnight recordings activated additional IED foci not seen during routine EEGs in 12 subjects. Four subjects had unilateral IEDs recorded during overnight recordings, and eight subjects had bilateral IEDs recorded during overnight recordings. In the context of other information (e.g., ictal recordings, neuroimaging studies), these sleep-activated IED foci may provide useful clinical information in the presurgical evaluation of patients refractory to AEDs. Adachi et al. (28) examined the predictive value of NREM sleep recorded on routine EEGs in 83 subjects with temporal lobe epilepsy who were seizure free for >1 year. They reported that the accuracy of EEG recordings for prediction of lateralization increased from 51.8% during waking to 78.3% during sleep, suggesting that IEDs occurring in non-REM sleep provide more accurage information for lateralization of epileptogenesis than do those occurring during waking (28). In contrast, Sammaritano et al. (8), examining sleep recordings in 40 subjects with temporal lobe epilepsy, concluded that localization of the primary epileptogenic area was more reliable in REM sleep than in wakefulness and least reliable in NREM sleep. Overnight sleep recordings are more likely than routine EEGs to contain NREM stage 2 sleep and especially NREM stages 3/4 sleep and REM sleep. Further investigations are necessary to determine the contribution of sleep recordings to the epilepsy surgery evaluation and the localizing role of NREM versus REM sleep.

In summary, our findings support the hypothesis that processes related to NREM sleep state and to the deepening of NREM sleep activate focal IEDs. Our results complement ongoing experimental studies and also illustrate the usefulness of applying logistic-regression methods to the characterization of the sleep–epilepsy relation.

Acknowledgment: This study was supported by NINDS 1 K08 NS01840 (Clinical Investigator Development Award) and University of Michigan General Clinical Research Center Grant M01-RR00042. Kenneth Morton and Judy Wiebelhaus assisted with EEG-polysomnography, Nichole Carlson and Michael Kallan assisted with statistical analysis, and Robert Bowes assisted with data review and the preparation of Fig. 1.

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