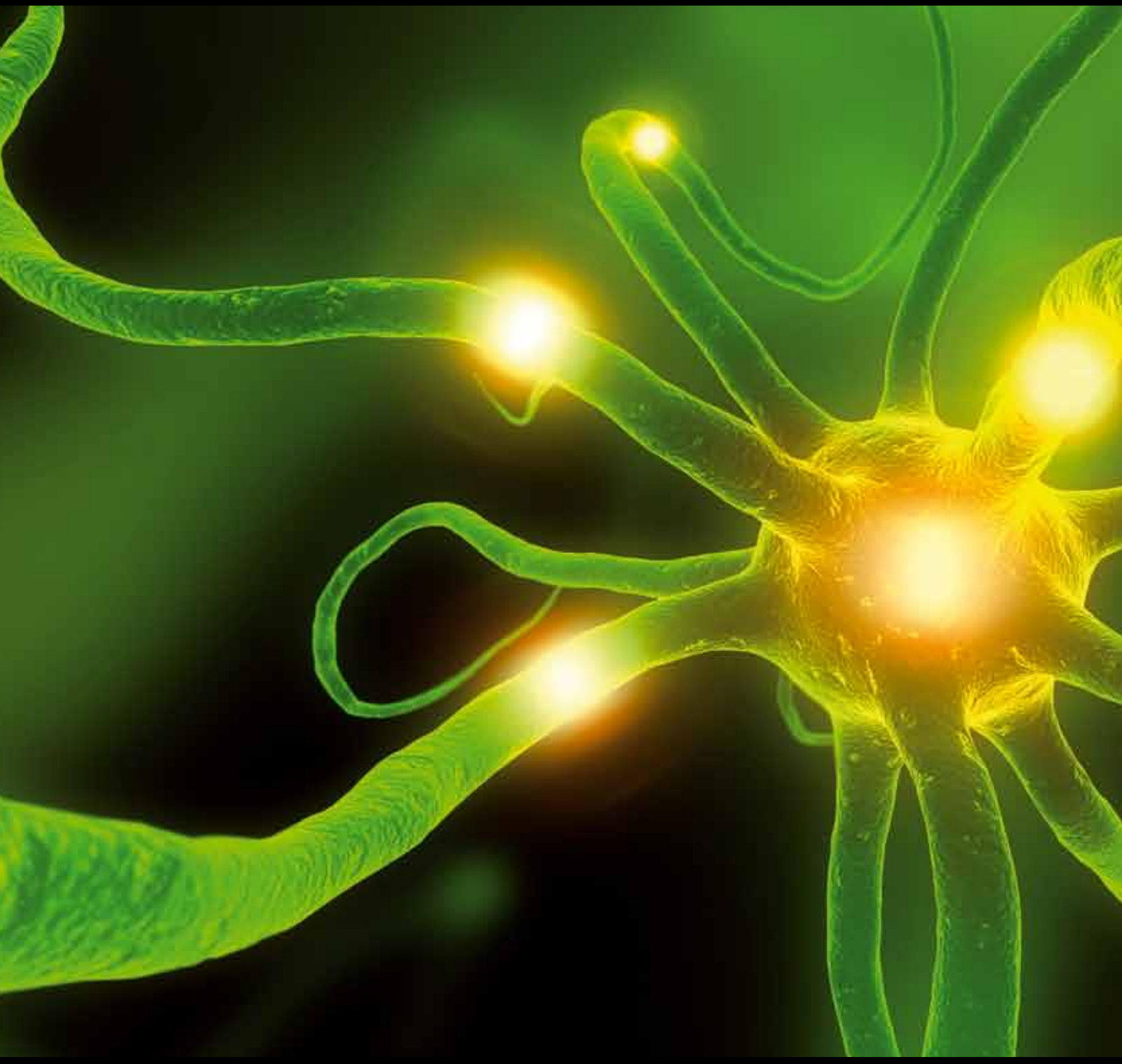
Epilepsy Research and Treatment

Sleep and Epilepsy

Guest Editors: Andrea Romigi, E. Bonanni, and M. Maestri



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Editorial Board

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Editorial
Sleep and Epilepsy

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"Of all the joys which are slowly abandoning me, sleep is one of the most precious, though one of the most common, too. A man who sleeps but little and poorly, propped on many a cushion, has ample time to meditate upon this particular delight. I grant that the most perfect repose is almost necessarily a complement to love, that profound rest which is reflected in two bodies. But what interests me here is the specific mystery of sleep partaken of for itself alone, the inevitable plunge risked each night by the naked man, solitary and unarmed, into an ocean where everything changes, the colors, the densities, and even the rhythm of breathing, where we meet the dead . . ." [1].

Sleep is crucial to the health and well-being of all individuals, and is of particular relevance to patients with epilepsy. Sleep deprivation, daytime sleepiness, but also normal sleep *per se*, well-known potential triggers for seizures are themselves influenced by epilepsy in a sort of mutual effect. Comorbidities and pharmacological treatment are other commonly accepted major factors that influence this interplay.

In clinical practice, patients with epilepsy are usually referred to sleep centers for either a specialistic evaluation of comorbid sleep disorders and a differential diagnosis between nocturnal seizures and parasomnias. Nonetheless, disrupted nocturnal sleep, excessive daytime sleepiness, and severe insomnia are common and frequently overlooked in these patients [2]. Sleep-related breathing disorders represent more than a simple comorbidity and should be considered a possible factor of pseudoresistance to antiepileptic treatment [3]. Sleep disruption may also worsen the neuropsychological outcomes in a population that has already an increased risk for cognitive and memory impairment. Diagnosing sleep alterations and sleep comorbidities in these patients is mandatory since these disorders are usually treatable or at least improvable by appropriate and individualized therapy.

As stated in a recent review [4], although the intimate relationship between sleep and epilepsy has long been recognized, our understanding of the underlining mechanisms still is incomplete.

We selected for these supplement novel research articles or reviews about key and controversial issues in this field. P. Halasz provides a critical review regarding recent advances in the mechanisms underlying sleep and epilepsy networks, and their pathophysiological interplay. The authors draw modern conceptual updates and cast new light on the cognitive consequences of both of these phenomena. P. Halasz and coworkers reviewed the literature pertaining the potential interference of epileptiform discharges on slow-wave activity and NREM sleep microstructure dynamics and their plastic functions during sleep.

As previously hinted, sleep and antiepileptic drugs (AEDs) represent another puzzling variable. AEDs are a key factor of the mutual interactions between sleep and epilepsy, given their potential negative influences on the sleep-wake cycle and daytime vigilance [5]. V. Shvarts and S. Chung review the large body of literature investigating AEDs effects on sleep and face the emerging and intriguing fields of chronobiology and chronotherapy. While most of the conventional AEDs impair nocturnal sleep and daytime vigilance, novel AEDs may have minor or even positive impact on the sleep-wake cycle [6, 7]. F. S. Giorgi et al.

present new clinical data on Lacosamide (a novel AED that acts selectively, enhancing slow inactivation of voltage-gated sodium channels) as an add-on therapy in a small cohort of drug-resistant epilepsy patients, finding no detrimental effects, on both subjective sleep quality and quantitative EEG parameters.

In addition, it is well known that sleep modulates interictal abnormalities. NREM sleep and sleep deprivation facilitate epileptiform discharges, whereas REM sleep decreases not only the spiking rate but also the spatial distribution of EEG abnormalities [8]. Nonetheless, some controversies are still present in this field, and three different papers in this supplement deal with these issues. M. Ng and M. Pavlova carry out an extensive review of the literature on the frequency of seizures during REM sleep, confirming the protective role of EEG desynchronization against interictal abnormalities, focal and generalised seizures, and specific epileptic syndromes (i.e., Benign Epilepsy of Childhood with Rolandic Spikes). The clinical significance of sleep deprivation is still debated. A. D. Negrillo critically reviews the influence of sleep and sleep deprivation on seizures and interictal discharges, paying special attention to the major mechanisms highlighting this mutual interaction. On the other hand F. S. Giorgi et al. deal with a large number of peer-reviewed papers, looking for the answer to a more pragmatic question. What is the real role of EEG after sleep deprivation in the difficult diagnosis process of epilepsy? Despite the observed high methodological variability, heterogeneity of epilepsy syndromes, and lack of recent works, the review strongly supports the role and usefulness of sleep deprivation as a diagnostic tool for epileptologists.

In conclusion, these six papers represent novel steps in the challenging field of the relationship between sleep and epilepsy, and focus on some intriguing, unclear, and clinically significant issues.

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M. Maestri

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Research Article

A Clinical-EEG Study of Sleepiness and Psychological Symptoms in Pharmacoresistant Epilepsy Patients Treated with Lacosamide

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Our aim was to evaluate the EEG and clinical modifications induced by the new antiepileptic drug lacosamide (LCM) in patients with epilepsy. We evaluated 10 patients affected by focal pharmacoresistant epilepsy in which LCM (mean 250 mg/day) was added to the preexisting antiepileptic therapy, which was left unmodified. Morning waking EEG recording was performed before ($t0$) and at 6 months ($t1$) after starting LCM. At $t0$ and $t1$, patients were also administered questionnaires evaluating mood, anxiety, sleep, sleepiness, and fatigue (Beck Depression Inventory; State-Trait Anxiety Inventory Y1 and Y2; Pittsburgh Sleep Quality Index; Epworth Sleepiness Scale; Fatigue Severity Scale). We performed a quantitative analysis of EEG interictal abnormalities and background EEG power spectrum analysis. LCM as an add-on did not significantly affect anxiety, depression, sleepiness, sleep quality, and fatigue scales. Similarly, adding LCM to preexisting therapy did not modify significantly patient EEGs in terms of absolute power, relative power, mean frequency, and interictal abnormalities occurrence. In conclusion, in this small cohort of patients, we confirmed that LCM as an add-on does not affect subjective parameters which play a role, among others, in therapy tolerability, and our clinical impression was further supported by evaluation of EEG spectral analysis.

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting up to two percent of the population worldwide. Many patients show recurrent seizures despite treatment with appropriate antiepileptic drugs (AEDs') [1, 2], and many experience AEDs side effects. In the last decades, new AEDs have been developed with the aim of balancing, as far as possible, significant efficacy with good tolerability.

Among them, Lacosamide (LCM) has been recently authorized in Italy and worldwide as a new add-on AED for the treatment of pharmacoresistant focal epilepsy.

Side effects of classical AEDs often involve cognitive functions, mood, and behavior to varying degrees, and this is the case also for newer AEDs (see, for instance, [3–5]). Unfortunately, a clear evaluation of these types of side effects in the single patient is often difficult because of the subjectivity of such complaints. This assessment is even harder in patients undergoing AED polytherapy.

It has been proposed by several authors the usefulness of a quantitative analysis on EEG in patients undergoing treatment with drugs acting on the CNS (for a review, see for instance, [6]), in this setting, abnormalities of EEG power spectrum have been interpreted as an objective measure of cognitive slowing/impairment (see, for instance, [7–9]). Furthermore, in the last decades, questionnaires specifically evaluating mood, anxiety trait, sleepiness, fatigue, and sleep quality have been developed.

The aims of the present study were (i) to analyze the effects of LCM on EEG in terms of EEG background spectra and interictal activity and (ii) to further evaluate LCM effects by using subjective questionnaires addressing

depression (Beck Depression Inventory-BDI), anxiety (State-Trait Anxiety Inventory-STAI), sleep quality (Pittsburgh Sleep Quality Index-PSQI), sleepiness (Epworth Sleepiness Scale-ESS,) and fatigue (Fatigue Severity Scale-FSS).

2. Materials and Methods

2.1. Patients and Study Design. Ten patients affected by focal epilepsy (6 males and 4 females, mean age 48.2 ± 14.8 years) were included in this study. The mean age at epilepsy onset was 13.5 ± 7.9 years. Five patients were affected by focal symptomatic epilepsy, and five were affected by probably focal symptomatic epilepsy. In Table 1, we reported a detailed description of etiologies, electroclinical features, and concomitant AEDs, as well as comorbidities.

The design of this study is a prospective open-label pragmatic one. We selected ten consecutive adult outpatients from our tertiary University Epilepsy Center who were fulfilling the following criteria: (a) being affected by partial focal epilepsy, not caused by a progressive etiology; (b) having experienced in the previous three months at least 12 seizures (not less than 2 for each single month); (c) having been treated with more than one appropriate AED, at adequate dose regimen; and (d) being screened for any kind of AV Block by at least a routine EKG.

Recruited Patients were submitted to video-EEG recording and clinical evaluation on the day before ($t0$) and at 6 months ($t1$) after beginning LCM.

LCM was administered to all of the enrolled patients at a starting dose of 50 mg/day, followed by biweekly 50 mg/day dose increase, up to each patient's maintenance dose on the basis of clinical response and tolerability (mean final daily dosage of 250 ± 81.6 mg/die). The remaining AED therapy was left unmodified throughout the study: in 9 patients, this included AEDs acting on voltage-gated Na+ channels (Table 1). Neurological examination and blood tests, including AED plasma levels, were monitored at $t0$ and $t1$; during these same visits, patients were administered the subjective questionnaires that were selected also based on previous studies in epilepsy patients [10–12] and are detailed below.

Starting at six months before $t0$, patients were asked to collect a detailed seizure diary, which were collected by the examiner at $t1$.

As shown in Table 2, there was a seizure reduction of 33.3% at $t1$ versus $t0$. In particular, 7/10 patients showed a seizure reduction at $t1$; in one, there was a slight seizure increase; four patients showed a seizure reduction ≥50%, and one of them was seizure-free at $t1$. When comparing raw seizure number at $t1$ versus $t0$, P was 0.068.

2.2. EEG Procedures. Each patient was admitted at our Sleep-Epilepsy Center for video-EEG monitoring session at $t0$ and $t1$ (see above).

Participants were instructed to follow their usual daily routine, meals, and caffeine consumption and to refrain from alcohol intake for 24 h before starting the recording. The EEG recordings were performed through a 32-channel cable video-telemetry system. Nineteen collodion-applied scalp-electrodes were placed according to the 10–20 system; chin electromyogram, electrocardiogram, and electrooculogram signals were recorded via additional skin surface electrodes. Electrode impedance was maintained below 5 kΩ. Filters were set at 0.1 and 30 Hz, and signal was notch filtered. Two additional electrodes were placed at mastoid level; for spectral analysis, only O1-mastoidal and O2-mastoidal traces were considered. All the EEG recordings were carried out with the same type of digital EEG equipment (BElite, EBNeuro, Florence), and data were acquired with a 258 bit sampling rate and stored on the PC hard disk for offline evaluation.

The EEG was recorded in a silent room of the University Sleep Center, during constant monitoring by an EEG technician.

The recording periods included (a) a night recording (polysomnography-PSG) from 9 p.m. to 7 a.m. of the following day (not shown) and (b) a routine video-EEG wake recording from 8 to 9.30 a.m. after the end of PSG.

On the morning 1.5 h video EEG recording, we performed an analysis of interictal epileptiform abnormalities (IIA) and power spectrum analysis of background activity.

In detail, we performed the following analysis of EEG data.

2.2.1. Interictal Abnormalities (IIA) Analysis. IIA occurrence was analyzed visually by two independent observers which were blinded, for each patient, as to whether they were scoring a $t0$ or $t1$ EEG tracing. The total number of IIA occurring during the 8–9.30 A.M. wake-EEG was recorded and converted to $n/10'$.

2.2.2. Power Spectrum Analysis. Epoch selection for qEEG analysis was performed offline on waking EEG recording obtained from 8 to 9.30 A.M. We selected randomly, and blindly to patient number and treatment, EEG periods lacking ictal and/or interictal abnormalities, movements artifacts, eye blinking, muscle activity or drowsiness signs. On these EEG parts, we used the fast Fourier transform (FFT), considering 2 minutes of EEG signal, automatically segmented by software into 2.56 s epochs. Analysis was performed for each frequency band: delta [1–4 Hz]; theta [4–8 Hz]; alpha [8–12 Hz], and beta [12–30 Hz].

Measures derived from FFT included (i) absolute power; (ii) percent relative power, and (iii) mean frequency.

We chose to analyze mainly the frequency in occipital derivation according to widely accepted criteria [6]. Moreover, the analysis of occipital recording allows the best identification of alpha activity, and recordings are devoid of artifacts observed in more anterior leads. To minimize statistical problems associated with multiple variables, results from the O1 and O2 leads were averaged for analysis.

2.3. Subjective Questionnaire. In order to evaluate the wake-sleep symptoms and psychological well-being of the patients included in this study, five scales were administered before and after 6 months of LCM therapy.

2.3.1. Beck Depression Index. BDI is a small questionnaire examining 21 symptom areas with a total score ranging from 0 to 63 proportionally to depression severity [13].

2.3.2. The State-Trait Anxiety Inventory. STAI is a brief self-administered questionnaire for the assessment of state and trait anxiety in adults and is composed of a State anxiety scale (STAI Y-1) and a Trait anxiety scale (STAI Y-2), consisting of 20 statements each [14].

2.3.3. Epworth Sleepiness Scale. ESS is the subjective scale that is generally considered as the gold standard for the evaluation of daytime sleepiness [15]. It evaluates individual degree of drowsiness in eight common daily conditions, has been validated in Italian [16], and is widely used in epilepsy [17]. It is generally accepted a cutoff of 10 as normal value [18].

2.3.4. The Pittsburgh Sleep Quality Index. PSQI is an instrument used to measure the quality and patterns of sleep in adults assessing seven domains self-rated by the subject [19] and already used also in epilepsy patients [20]. A global score of 5 or more reveals a poor quality of sleep and is considered as the cutoff from normal to pathological values.

2.3.5. The 9-Item Fatigue Severity Scale. (FSS) is one of the most commonly used self-report questionnaires to measure fatigue [21] with value ranging from 1 (strong disagreement with the statement) to 7 (strong agreement). A cut-off of 4 is generally considered [22].

2.4. Statistical Analysis. For IIAs, absolute power spectrum (for each frequency band), relative power spectrum (for each frequency band), mean alpha frequency, and seizure frequency, a Student's t-test analysis for paired data was applied to compare $t1$ and $t0$ data.

For scales (STAI, BDI, ESS, FSS, and PSQI), the score comparisons between $t1$ and $t0$ were performed by the Wilcoxon signed-rank test.

For all of the analyses, the null hypothesis was rejected when $P < 0.05$.

3. Results

3.1. Adverse Effects of LCM. LCM was not discontinued in any of the patients. Five patients complained mild drowsiness, and one patient experienced sleepiness, but these effects were transient and improved right after slowing the titration schedule. Blood levels of concomitant AEDs were not significantly affected by LCM administration (not shown).

3.2. Effects of LCM on EEG IIAs (Table 2). As shown in Table 2, in all but two patients we observed either a decrease or a lack of effect of LCM on IIAs. Patient 1 already at baseline showed a significantly higher IIA number (22.2) than the remaining ones (1.72 ± 0.65), and at $t1$, there was 14% increase in its occurrence. With the exception of these two patients, in all of the remaining ones there was no effect or a slight decrease in IIAs occurrence. The mean IIAs % change at $t1$ was −19.3% versus baseline.

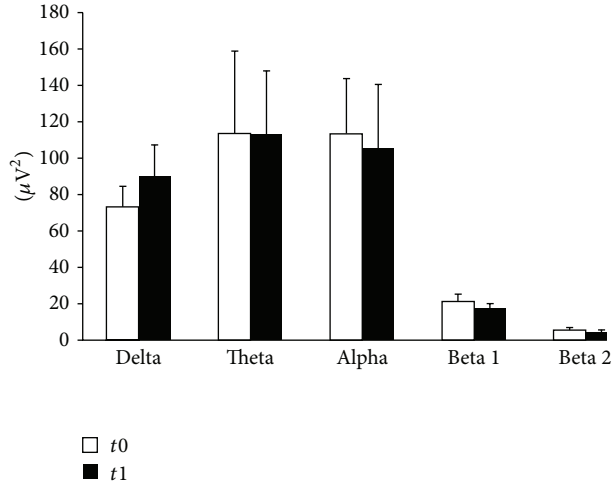

Figure 1: Power spectrum analysis of EEG. Patients were assessed at t0 and after 6 months ($t1$). The graph shows absolute power (μV^2) calculated on O2-Ref EEG traces. qEEG analysis was performed offline on waking EEG recording obtained from 8 to 9.30 A.M., randomly selecting EEG periods lacking ictal and/or interictal abnormalities, movements artifacts, eye blinking, muscle activity or drowsiness signs. On these EEG parts, we used the fast Fourier transform (FFT), considering 2 minutes of EEG signal, automatically segmented by software into 2.56 s epochs. Analysis was performed for each frequency band: delta [1–4 Hz]; theta [4–8 Hz]; alpha [8–12 Hz], and beta [12–30 Hz]. None of these bands were significantly affected by LCM treatment.

3.3. Effects of LCM on qEEG (Table 3 and Figure 1). Concerning qEEG, LCM did not significantly affect the absolute power density for any of the frequency intervals evaluated (Figure 1, Table 3), apart from a slight, nonsignificant increase in delta frequency representation. Similarly, alpha mean frequency was not affected by LCM administration, as well as the mean frequency of the remaining bands (Table 3).

PSG data concerning the night before EEG recording were analyzed in detail and are part of a separate multicenter study (in preparation); in any case, all PSG recordings showed a total sleep time longer than 6 hours, which is considered necessary for a proper evaluation of sleepiness in international guidelines [23], and no statistical differences were found between $t0$ and $t1$ for the variables of sleep continuity (i.e. sleep efficiency, total sleep time).

3.4. Psychological Effects (Tables 4 and 5). We did not observe any significant changes in BDI scores. Nevertheless, in four patients with intermediate BDI scores, we observed an improvement at $t1$ (patients 1, 2, 4 and 7). In patient #6 presenting a high BDI score at $t0$ (22), we did not observe any changes at $t1$.

Similarly, in the STAI scales the scores remained stable throughout the observation period.

Table 1: Demography.

Patients	Age	Age at onset (yr)	Epileptic syndrome	Seizure type	AEDs before-LCM
No. 1	45	11	Symptomatic temporal lobe epilepsy (posttraumatic)	Focal limbic seizures, SG	OXC 900 mg/die; LEV 3 g/die; VPA 1,5 g/die; LTG 200 mg/die; TPM 600 mg/die; VNS
No. 2	34	13	Symptomatic temporal lobe epilepsy (postradiotherapy calcification)	Focal limbic seizures, SG	OXC 1200 mg/die; LTG 300 mg/die; LEV 3 g/die; VNS
No. 3	34	18	Probably symptomatic temporal lobe epilepsy	Focal limbic seizures, rarely SG	LEV 3,5 g/die; ZNS 200 mg/die; TPM 600 mg/die; CBZ 1600 mg/die
No. 4	76	16	Probably symptomatic frontal lobe epilepsy	Focal seizures	CBZ CR 1200 mg/die; PB 50 mg/die; LTG 200 mg/die; ZNS 450 mg/die
No. 5	43	13	Probably symptomatic temporal lobe epilepsy	Focal limbic seizures	OXC 1800 mg/die; LEV 3 g/die
No. 6	59	6	Probably symptomatic temporal lobe epilepsy	Focal limbic seizures	ZNS 100 mg/die; LEV 1 g × 3/die; OXC 600 mg × 3/die
No. 7	55	10	Symptomatic temporal lobe epilepsy (left HS)	Focal limbic seizures	LEV 2 g/die; OXC 2100 mg/die; TPM 300 mg/die
No. 8	51	25	Symptomatic temporooccipital epilepsy (right retrotrigonal lesion)	Focal limbic seizures	LEV 1 g × 3/die; CBZ 600 + 400 + 600; ZNS 200 mg/die
No. 9	26	1	Symptomatic frontal lobe epilepsy (calcifications of falx cerebri)	Nocturnal frontal seizures	CBZ 1200 mg/die; TPM 450 mg/die
No. 10	59	27	Probably symptomatic temporal lobe epilepsy	Focal limbic seizures	TPM 350 mg/die

HS: hippocampal sclerosis; SG: secondarily generalized; CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; TPM: topiramate; VNS: vagus nerve stimulation; VPA: valproic acid; ZNS: zonisamide.

Table 2: Interictal EEG abnormalities and seizures frequency after LCM.

Patient	IIAs/10 min $t0$	IIAs/10 min $t1$	% variation IIAs in ($t1 - t0$)	Seizures/month $t0$	Seizures/month $t1$	% variation seizure in frequency ($t1 - t0$)
No. 1	22,22	25,77	+14	15,16	7,66	−50
No. 2	2,44	1,55	−37	4,66	0	−100
No. 3	1,44	0,77	−45	4	3,16	−21
No. 4	0,33	0,22	−34	22,16	9,16	−59
No. 5	0,88	1	+12	10,16	7,16	−30
No. 6	0,44	0,44	0	3,83	4,33	+12
No. 7	0,77	0,55	−29	4,33	4,33	0
No. 8	0,66	0,44	−34	9,83	7	−29
No. 9	6,66	6,44	−4	54,16	24,16	−56
No. 10	1,88	1,22	−36	3,66	3,66	0
Pooled	3,77 ± 2,13	3,84 ± 2,50	−19,3	13,19 ± 4,94	7,06 ± 2,07	−33,3

Values in bottom row concerning columns 2, 3, 4, and 6 are expressed as mean ± S.E.M.
IIAS: interictal EEG abnormalities.

At baseline, excessive daytime sleepiness (ESS score ≥10) was reported by two patients. Six months after LCM therapy, two other patients had pathological scores at ESS. However, no patients reported severe daytime sleepiness, that is, ESS > 14, and when measuring the group mean values, no statistical differences were observed. Also, FSS showed no differences between $t1$ and $t0$, even if it was higher than normal ranges in both conditions. Concerning PSQI, the percentage of "good sleepers" (i.e., with a score <5) was 50% at $t0$ and 80% at $t1$. Table 5 shows mean values for each PSQI subitem at $t0$ and $t1$.

4. Discussion

In this small cohort of pharmacoresistant focal epilepsy patients, we investigated the effects of LCM in terms of EEG and psychological effects. We showed that LCM does

Table 3: Power spectrum analysis of EEG.

	Delta			Theta			Alpha			Beta 1			Beta 2		
	$t0$	$t1$	P	$t0$	$t1$	P	$t0$	$t1$	P	$t0$	$t1$	P	$t0$	$t1$	P
Absolute power (μV^2)															
Median	67,145	85,195		53,5	79,395		91,52	70,635		16,125	15,61		4,165	2,92	
Mean	73,0263	89,97	0,42	113,5075	112,9513	0,99	113,3288	105,4775	0,86	21,1188	17,4675	0,47	5,6913	4,3488	0,47
S.E.M.	11,4714	17,2173		45,4567	34,8912		30,1147	34,9935		4,2976	2,4071		1,4159	1,1695	
Relative power															
Median	25,31	28,68		20,15	26,995		31,595	28,37		7,075	5,96		1,415	1,07	
Mean	26,0737	29,2212	0,61	28,2462	30,2275	0,81	33,6137	31,845	0,82	7,9887	6,3487	0,49	2,4275	1,6562	0,45
S.E.M.	4,2267	4,3531		7,0544	4,6986		5,388	5,1308		2,08	1,0074		0,8032	0,5687	
Mean frequency (Hz)															
Median	1,59	1,645		6,22	6,365		9,12	9,07		14,13	13,955		19,9	19,93	
Mean	1,61	1,6113	0,99	6,2087	6,2763	0,74	9,3	9,2113	0,73	14,1525	13,9425	0,12	20,0525	20,0525	0,99
S.E.M.	0,0582	0,0826		0,1541	0,1204		0,18	0,1813		0,0999	0,0816		0,1304	0,1237	

Table 4: Psychological effects of lacosamide.

	Score at $t0$ (mean ± S.D.)	Score at $t1$ (mean ± S.D.)	P
PSQI	4,4 ± 1,6	3,7 ± 1,3	0.23
ESS	7,7 ± 1,8	8,3 ± 2,4	0.25
FSS	40,4 ± 12,1	36,7 ± 13,5	0.26
BDI	12,1 ± 5,1	9,9 ± 4,4	0.07
STAI Y1	41,1 ± 7,6	39,1 ± 5,9	0.08
STAI Y2	43,7 ± 10,1	42,2 ± 10,9	0.15

Statistical analysis was performed by means of Wilcoxon signed-rank nonparametric test.
BDI: Beck Depression Inventory; ESS: Epworth Sleepiness Scale; FSS: Fatigue Severity Scale; PSQI: Pittsburgh Sleep Quality Index; STAI Y1: S-anxiety scale of the State-Trait Anxiety Inventory form Y; and STAI Y2: T-anxiety scale of the State-Trait Anxiety Inventory form Y.

Table 5: Effects of lacosamide on the different subitems of Pittsburgh sleep quality index.

	Score at $t0$ (mean ± S.D.)	Score at $t1$ (mean ± S.D.)	P
C1 subjective sleep quality	0,9 ± 0,6	0,7 ± 0,5	0.5
C2 sleep latency	0,4 ± 0,5	0,3 ± 0,5	0.68
C3 sleep duration	0,8 ± 0,4	0,8 ± 0,4	1
C4 sleep efficiency	0,6 ± 0,5	0,5 ± 0,5	0.9
C5 sleep disturbances	1,2 ± 0,8	0,9 ± 0,7	0.34
C6 use of sleeping medication	0,2 ± 0,4	0,3 ± 0,5	0.59
C7 daytime dysfunction	0,3 ± 0,5	0,2 ± 0,4	0.68

Statistical analysis was performed by means of Wilcoxon signed-rank nonparametric test.

not affect significantly EEG background in terms of power spectra, nor does it worsen depressive or anxiety traits, as well as subjective indices of sleepiness, fatigue, and sleep quality in this type of patients. Furthermore, LCM did not affect IIAs occurrence significantly, despite its efficacy on seizures.

We chose a prolonged observation period (6 months from $t0$ to $t1$) in order to allow (a) a prolonged slow titration of the LCM; and (b) a complete stabilization of the effects of the drug on both EEG and clinical conditions.

The effect of LCM was much lower on IIAs than toward seizures and not remarkable. This is not surprising, since previous studies failed to show a parallelism between seizure and IIAs frequency concerning other AEDs, such as carbamazepine [24] and gabapentin [25] in focal epilepsy. Incidentally, an elegant experimental study performed in amygdala kindled cats confirmed the lack of an effect of carbamazepine on spike occurrence, despite a significant effect on seizures [26]. Conversely, topiramate [27] and lamotrigine [28] have been shown to reduce IIAs incidence and spreading, in parallel with seizure occurrence. The lack of a correlation between IIAs reduction and seizure frequency we observed in our study might be due to the pharmacodynamic effects of LCM itself. However, further experimental studies would be needed to address this hypothesis.

When deciding to add a new AED in pharmacoresistant epilepsy patients, the main concern of the prescribing physician is to get the maximum efficacy with the lowest incidence of side effects. Among the main complaints of pharmacoresistant epilepsy patients in terms of AED tolerability, there are drowsiness, confusion, and dizziness, as well as mood changes and anxiety.

The low incidence of CNS side effects after LCM we found in our study, as well as the complete lack of dropout during follow up, might be due to the design of our study indeed; in fact, the titration of LCM was shaped on patients' tolerability and efficacy, and the long follow-up period (6 months) allows a full stabilization of the appropriate drug regimen.

Several authors have proposed that EEG background correlates with the degree of alertness and of cognitive performances (for a detailed review, see [29]); even though such a link is indirect and difficult to quantify, many investigators agree on a solid correlation of slowing of alpha mean frequency with cognitive impairment (see, for instance, the reviews by [30, 31]). We could not show any significant reduction of alpha activity at $t1$ versus $t0$ nor an increase

in the representation of slower frequencies (i.e. delta and theta ones). This is in agreement with the lack of subjective significant complaints reported by our group of patients, both in terms of drowsiness, and in terms of increased cognitive impairment, as compared with baseline. Potentially, the EEG derivations we used (occipital ones) for spectral evaluation are mainly suitable for alpha band analysis, as compared with lower frequency bands, while for slower bands the analysis of additional derivations might be preferable, and this might be a limitation of our study. However, nevertheless we chose to focus on occipital derivations since these are the only ones used also in many similar studies in which significant EEG modifications were observed during AEDs treatment (e.g., [7–9]), while data assessing also other derivations in these types of studies are more sparse and difficult to compare with each other.

Previous studies assessing power spectral analysis in epileptic patients were performed in focal epilepsy populations, either drug free [31] or during AED monotherapy [7, 9, 32–34] or polytherapy [35]. Further, AEDs effects on EEG background have been evaluated also in healthy volunteers [8, 36].

In our study, we did not find, for anyone of the frequency band tested, a difference between $t0$ and $t1$, with this being in line with the effect of other AEDs, such as phenobarbital, lamotrigine, and valproic acid [28, 33, 35]. Conversely, previous studies in patients treated with the sodium-channel blocking AEDs CBZ and OXC showed a decrease of alpha mean frequency [7, 24, 33]. Thus, our findings suggest that the enhancing effects of LCM on voltage-gated sodium channels slow inactivation affects neocortical rhythm in a different manner as compared with the effect of fast-inactivation enhancement. The lack of any significant effect we observed on qEEG might have been due to the fact that already at baseline EEG background was significantly affected both by the underlying disease and by the concomitant AEDs. However, indeed our aim was not to compare our data with those of a control population (since our subjects were not healthy volunteers taking LCM) but to show, if any, the existence of a worsening potential effect of LCM on EEG background in the particular population of patients who are affected by pharmacoresistant epilepsy. Furthermore, we found mean variability in the different frequency bands similar to those observed by other authors in AED monotherapy (see for instance [7, 33, 34]).

AEDs bear, to varying degrees, psychological effects including effects on mood and anxiety [3, 37, 38]; furthermore, it has been shown that the incidence of such adverse effects increases in parallel with the number of ongoing AEDs [3]. In this study, patients were administered with BDI to address depressive features, which is a well-validated scale that has been used extensively in such populations before [10, 39]; this scale was not significantly affected by adding LCM. Anxiety is another one of the commonest complaints in patients undergoing antiepileptic therapy (see [3, 5]); we showed that STAI questionnaires, which explore anxiety trait and state and have been validated in several populations affected by chronic neurological illnesses [39–41], are not modified by LCM add-on. However, it should be noted that both depressive and anxiety features at $t0$ were slightly elevated in our patients as compared to control populations from our lab historical data (not shown). This might affect the finding of no effect of LCM add-on on these measures. However, as said, the aim of this study was to assess, indeed, the additional effect of LCM on a category of patients already bearing a burden of potential side effects of different drugs and of the disease itself as well.

Concerning sleep-wake cycle, our study shows that subjective standardized scales did not highlight significant changes when LCM was added to previous therapies. As concerns sleepiness, in the registration studies, LCM showed a risk of sleepiness as a side effect (3.1% when considering differences towards placebo), which is lower than other new AEDs (see as a review, [42]). An exhaustive discussion about subjective evaluation of sleep, sleepiness, and fatigue in pharmacoresistant epilepsy patients is complex and far beyond the aim of this study; it is worth noting that the ESS and PSQI scores in our patients are within normal range, while FSS showed higher levels of fatigue than usually reported in general population, but without statistically significant changes during LCM therapy.

A discrepancy between objective and subjective evaluation of sleep and sleepiness in epilepsy has been suggested, and we could hypothesize that single patients could underestimate the degree of these disturbances, since these could be chronic symptoms, and subjects could be more focused on seizure frequency and on daytime fatigue. Moreover, the subjective differentiation between sleepiness and fatigue is complex and not completely understood ([43]).

Thus, a study using objective standardized methods (i.e. polysomnography and multiple sleep latency test) to evaluate sleep and sleepiness would be necessary to further understand the impact of LCM on these aspects.

5. Conclusions

In this study, we observed that our clinical impression of tolerability of LCM as an add-on was further significantly supported by objective EEG measures and by semiquantitative analysis of effects on sleepiness, mood, and anxiety, even though therapy tolerability as a whole is due also to many aspects not specifically evaluated in this paper.

We are aware that this study was not randomized in design and the patients were under previous AEDs. However, since we compared the chronic effects of LCM versus each patient's own baseline and throughout an observation period of 6 months, this makes our findings interesting, since they reflect closely a typical clinical setting of patients taking LCM.

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Review Article

How Sleep Activates Epileptic Networks?

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Background. The relationship between sleep and epilepsy has been long ago studied, and several excellent reviews are available. However, recent development in sleep research, the network concept in epilepsy, and the recognition of high frequency oscillations in epilepsy and more new results may put this matter in a new light. *Aim*. The review address the multifold interrelationships between sleep and epilepsy networks and with networks of cognitive functions. *Material and Methods*. The work is a conceptual update of the available clinical data and relevant studies. *Results and Conclusions*. Studies exploring dynamic microstructure of sleep have found important gating mechanisms for epileptic activation. As a general rule interictal epileptic manifestations seem to be linked to the slow oscillations of sleep and especially to the reactive delta bouts characterized by A1 subtype in the CAP system. Important link between epilepsy and sleep is the interference of epileptiform discharges with the plastic functions in NREM sleep. This is the main reason of cognitive impairment in different forms of early epileptic encephalopathies affecting the brain in a special developmental window. The impairment of cognitive functions via sleep is present especially in epileptic networks involving the thalamocortical system and the hippocampocortical memory encoding system.

1. Introduction

The robust activation of epileptic interictal and ictal activity in NREM sleep is well known and valid for almost all types of epilepsies. Different aspects of relationship between sleep and epilepsy were addressed in several excellent reviews [1–4]. During development of the last years, several new aspects have been elaborated contributing to understand better the activation of interictal and ictal epileptic phenomena by sleep.

The most important issues among them are as follows. (1) Sleep physiology has revealed neuronal networks governing wake-sleep alternations and cyclic changes during night sleep. Nowadays we see better the interrelationship between the sleep-wake circuitry and its multifold relationship with the different epileptic networks. (2) In the microstructure of sleep certain dynamic key points have shown to be associated with epileptic activation identified within the system of cyclic alternating pattern (CAP) correlating with reactive slow wave events. (3) One of the most important among recent discoveries is the exploration of the high frequency range of EEG and the recognition the relationship of this phenomenon with epilepsy and slow wave sleep. (4) Recognition of epileptic encephalopathies have shown that within a certain developmental window epileptic activity-usually during sleep-takes over the conduction in important physiological systems, and by the principle of "firing together-wiring together" epilepsy is hijacking physiological functions. (5) Underlying point 4 the key mechanisms by which interictal epileptic activity during slow wave sleep is interfering with cognitive functions have been increasingly studied.

Research Background

Sleep Research

Anatomy, Neurochemistry, and Dynamic Interaction of Wake and Sleep Promoting Circuits. The existence of two antagonistic systems promoting sleep and wake state was assumed already in 1930 by von Economo [5] based on autopsy findings of victims of European encephalitis letargica pandemia. He proposed that region of the hypothalamus near to the optic chiasm should contain sleep promoting, and the posterior hypothalamus wake promoting neurons.

From the forties of the last century the concept of an ascending "arousal system," maintaining wakefulness, in the brainstem of animal and human brain, became more and more clear [7]. The several transmitters (acetylcholine, noradrenalin, serotonin, catecholamine, histamine, and orexin) serving detailed functional properties of this system were also step by step revealed [8–10].

At the turn of the 20/21 century, Saper and coworkers [6] and others [12] showed that the ventrolateral preoptic area (VLPO and extended VPLO) send GABA-ergic and galanin-ergic inhibitory impulses to all the brainstem nuclei harbouring the ascending pathways of the arousal systems and keep firing throughout the whole NREM sleep, providing the substrate of the "sleep system" with opposite function to the "wake system." Later it turned out that nuclei of the arousal system also exert inhibitory effect on the "sleep promoting" preoptic neurons. "When VLPO neurons fire during sleep, they would inhibit the arousal system cell groups thus disinhibiting and reinforcing their own firing. Similarly when arousal neurons fire at high rate during wakefulness, they would inhibit the VLPO, thereby disinhibiting their own firing" [6]. This reciprocal relationship is nowadays more or less accepted as the elementary hypothalamic "sleep switch" module underlying alternations of sleep and wake state (Figure 1).

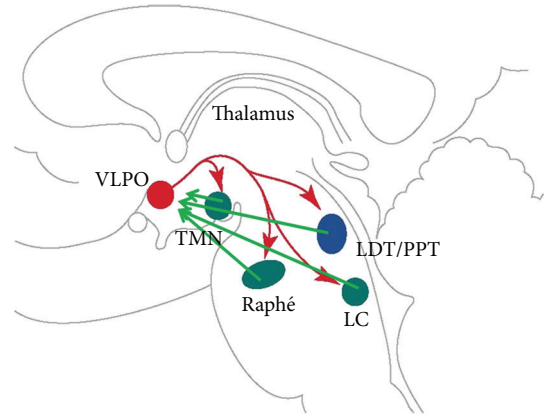


Figure 1: Brainstem-hypothalamic sleep-wake system. VPLO represents sleep promoting neuronal assemblies exerting inhibitory influence (red) on arousal promoting ascending pathways. Arousal system originating from different nuclei working with different transmitters (LC = locus coeruleus, adrenergic, raphe nuclei, serotoninergic, TMN = tuber mamillare, histaminergic, LDT/PPT: = lateral dorsal tegmental/pedunculopontine, cholinergic) exerts reciprocal inhibitory influence on VLPO sleep promoting neurons. (modified after Saper et al., 2001 [6]).

NREM Physiology Underlain by the Special Burst-Firing Working Mode of the Thalamocortical System. The inhibition of the arousal systems by the extended VLPO system has a further consequence, namely, the liberation of the thalamocortical system, because during wake state the arousal systems exert tonic cholinergic inhibition on the thalamocortical system. Liberation of the thalamocortical system is reflected by widespread development of spindling, delta activity, and slow (below 1 Hz) oscillation as characteristic by-products of the complex interrelationship of cortical (pyramidal cells), thalamic (relay neurons), and reticular (nucleus reticularis thalami (NRT) constituents of the system).

During wakefulness, the system works as a relay centre which faithfully conveys input from the outer world towards the cortex. This is executed by the so-called "tonic activity" of the network reflected by desynchronized EEG.

When we go to sleep, a cascade of events starts, and the working mode of the thalamocortical system is going to change toward an excitatory-inhibitory cycle, namely, burst-firing mode in which the nucleus reticularis thalami periodically inhibits firing of the thalamic relay nuclei, and this sequence is reflected on the cortex either as spindles or as deltas depending on the level of membrane polarisation of the relay cells. Thalamic structures isolated from NRT do not show oscillatory behaviour, while the NRT produce spindling even after isolation from the rest of the thalamus [13].

A further player of slow wave sleep: the slow oscillation below 1 Hz had been described in the nineties (in cats by Steriade et al. 1993 [14] and in humans by Achermann and Borbély [15]). The cortical nature and widespread presence throughout the cortical mantle were proven by several studies [14, 16, 17]. The slow oscillation consists of a depolarizing and hyperpolarizing phases, namely "up" and "down states." While the up state is characterized by rich neuronal and synaptic activity, and contains high frequencies, during the down state the cortical network is globally disfacilitated.

Studies of NREM sleep rhythms clearly showed that they are closely interconnected appearing in coalescence. The depolarized part (up-state) of the slow oscillation below 1 Hz envelops delta rhythm and spindling together with gamma and ripple degree fast activity [20, 21]. Combinations of spindles, K-complexes, and delta activity with fast rhythms are the product of interplay between cortical and thalamic structures within the thalamocortical system.

Dynamic Structure of NREM Sleep Fuelled by Reactive Phasic Changes Related to Arousal Influences. Exploration of the so-called "microstructure" of NREM sleep [22] revealed that stages of sleep (standardized by Rechtschaffen and Kales) consist of continuous fluctuations which are kept in motion by phasic changes called "microarousals" (reflected by EEG changes, autonomic signs, and muscle activity without awakening). These reactive phasic events (elicitable by sensory stimuli and assumable appearing as a reaction to some external (or internal) stimuli) create abundant fluctuations, lend flexibility to the sleep structure by which microfluctuations led to the development of macrofluctuations (stage shifts), and ensure a flexible connection between the sleeper and the surrounding world.

In the mid-eighties, Terzano and coworkers discovered a hitherto not recognized long-term cyclicity during NREM sleep related to sleep perturbations, namely cyclic alternating pattern (CAP) [23].

The CAP cycle consists of two phases: a phase A and a phase B. Phase A is mostly identical with the phasic activation events (see below for more details), while phase B is characterized by the background level of the sleep stage (Figure 2).

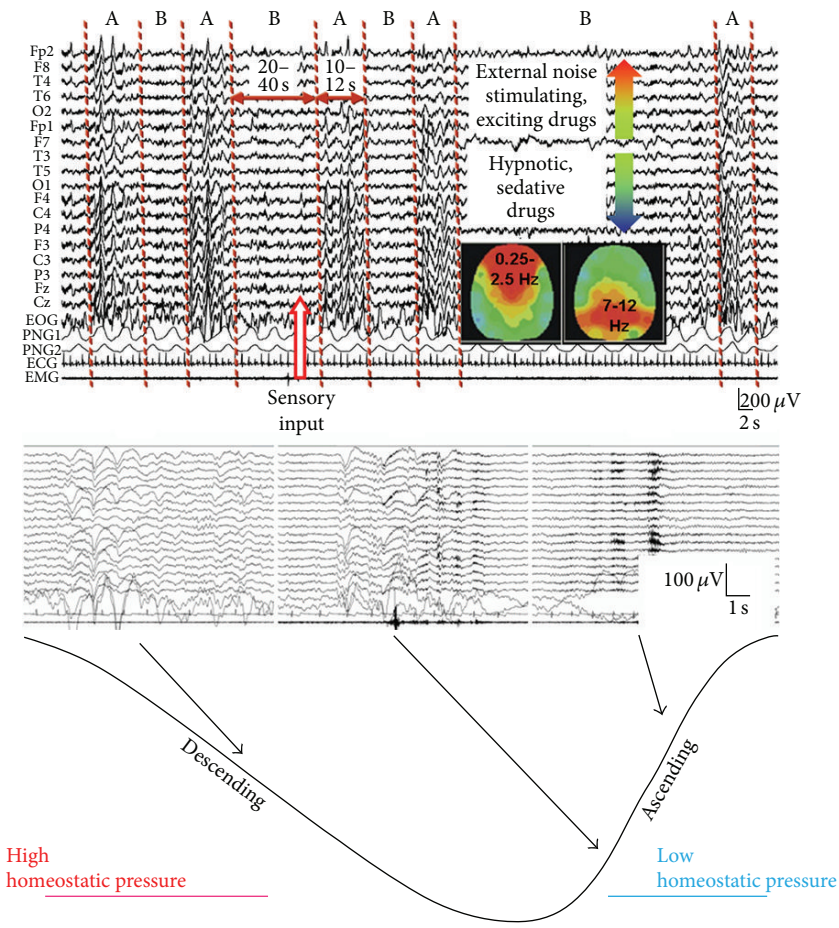


Figure 2: Schematic features representing the Cyclic Alternating Pattern (CAP) phenomenon. Above: alternation of activated (a) and background (b) episodes with characteristic parameters. In the middle: electrographic features of three kinds of A phases (A1-A2-A3). Below: schematic representation of the sleep cycle with descending and ascending slopes. A1 type phasic activation is associated with the high homeostatic pressure periods of sleep cycles, while A2 and mainly A3 type phasic activities are associated with low homeostatic pressure periods of sleep cycles.

Sensory stimuli in phase B are able to elicit the phase A pattern. In CAP, the arousal-dependent phasic events are arranged in complex pseudoperiodic assemblies. The mean period time between two A phases is about one minute. The average phase A duration is 10–12 sec, while the average length of phase B is 20–30 sec. According to the type of activation reached by phase A, three categories can be differentiated.

Phase A1 type comprises exclusively synchronization patterns (alpha in stage 1, sequential K-complexes in stage 2 and superficial stage 3 and reactive slow wave sequences in stages 3 and 4). It is identical with the synchronization-type microarousals [24].

On a slightly higher level of arousal, phase A2 type is composed of microarousals preceded by synchronization composed by K-complexes or slow waves, followed by either sigma or alpha and delta stretches.

On the highest level of arousal, the phase A3 type will be a microarousal without slow waves. This is identical with the traditional desynchronisational microarousal [25] (Figure 2).

The percentage of CAP time in NREM sleep (CAP rate) is age related. The CAP rate is high in very early infancy (up to 100% of NREM sleep in the newborn in the form of "trace alternant"). It declines to 44% among teenagers and diminishes to 25–30% in young adults. It then increases to an average of 54% in older age groups. The CAP rate correlates negatively with the subjective evaluation of the quality of sleep (the higher the CAP rate, the poorer the quality of sleep). The CAP rate is also increased by external noise and lowered by prolonged sleep deprivation. Stimulating and arousing drugs increase and hypnotic/sedative drugs decrease the CAP rate. The power spectral analysis of CAP phenomena revealed [26] that CAP corresponds to periods in which frontal dominant very slow delta activity groups together a range of different EEG activities. Distribution of the different phase A subtypes proved to be different across the sleep cycles. On the descending (D) slope and especially in the first cycles phasic activity is less frequent and characterised by synchronisation type and sleep-like slow wave answers (A1 type), associated with mild autonomic

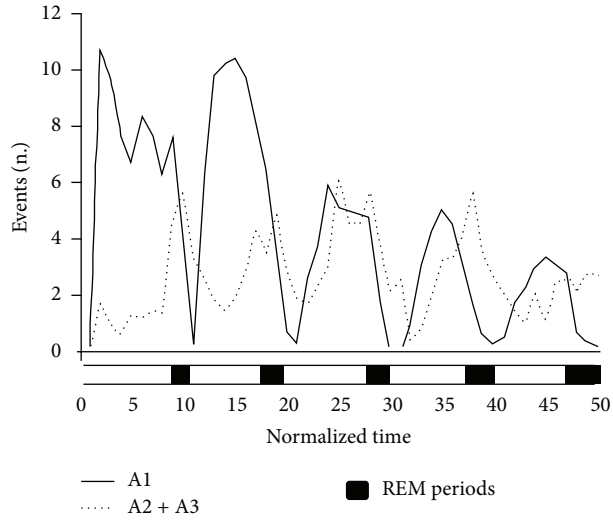


Figure 3: Different distribution of CAP A1 and A2-3 phases across night sleep. The distribution of A1 phases follows the classical pattern of slow wave decline from evening to morning predicted by the behaviour of the S-process of Borbély. The distribution of A2-3 phases has a different course; their amount do not decrease from evening to morning and show recurrent peaks before and during REM sleep (modified after Terzano et al., 2005 [11]).

perturbations. On the ascending (A) slope phasic activity is more frequent, and both the EEG morphology and the concomitant autonomic changes correspond more to the conventional A2 and A3 type phasic activation [27].

CAP is an integrated part of the NREM sleep slow wave activity. Since 30–40% of sleep time is spent in CAP A phase (CAP rate) and A1 phase is more than 60% of all the CAP sequences, reactive slow activity in the form of A1 phase is a considerable amount of sleep slow waves. CAP A1 rate in NREM sleep undergoes a characteristic significant exponential shape reduction from the beginning to the end of sleep [11]. It is parallel with the behaviour of the slow wave activity course across the night and with the homeostatic S process of Borbély [28] furthermore congruent with the dampening course of K-complex rate during sleep [29]. At the same time, rate of phase A2-3 showed quite different distribution with cyclic peaks before the REM periods on the ascending slopes of cycles, without any dampening during the course of sleep (Figure 3).

The tuning of sleep-wake balance probability lies in the relationship between the reciprocal antagonistic wake promoting ascending arousal systems and sleep promoting VLPO system, and CAP sequences reflect the balance between sleep and wake promoting systems. When VLPO system exerts GABA-and galanin-ergic inhibitory influence and keeps firing in a certain rate during sleep, the inhibitory influence of the arousal system dissipates. When a phasic arousal influence is arriving, the VLPO system became transitorily weakly inhibited, but if the arousal influence does not continue, the VLPO system became again liberated fuelling the backinhibition of the arousal system producing (quasi rebound) sleep phenomena (CAP A1 phase). This situation is valid especially when on the descending slopes of first cycles; the VLPO system is prevailing (during high homeostatic pressure), and the arousal system is weak. During the third part of sleep on the ascending slopes of the cycles, the situation is different: the VLPO system is less active in inhibiting the arousal system; therefore, the arousal impulses activate easily the cortex, and these phasic arousals achieve more prominent arousal in the form of CAP A2 and A3 responses driving the sleeper toward more superficial vigilance states.

NREM Sleep Homeostasis Serves Plastic Changes and Recuperation of Cognitive Functions. In the last 10–15 years, local aspects of homeostatic regulation receive more and more attention. Beyond the classical knowledge of previous wake state proportional delta power increases during the next night, and the frontal preponderance of sleep slow activity and further the frontal dominance of the recovery increase after sleep deprivation, and dominant hemisphere preponderance was emphasized in several studies [30, 31]. Increasing lines of evidence support the role of slow wave sleep in human frontal cognitive functions [32]. Beside the frontal localization in homeostatic regulation associated with certain cognitive functions, different kinds of "use-dependent" increase of regional slow wave activity have been registered after particular functional usage. Extensive sensory stimulation of one arm before sleep led to an increase of delta power in the opposite hemisphere over the somatosensory arm area [33]. An opposite intervention: immobilization of the arm caused a local reduction of delta power in the same localization [34]. In the light of these experiments delta power of sleep seems to depend on the amount of afferent activity or in other experiments on the degree of learning-related change in synaptic strength before sleep [32]. Stickgold and coworkers [35] have confirmed that some learning (texture discrimination task) occurs only after a night of sleep. Sleep-deprived subjects fail to improve on texture discrimination even after two recovery nights. The phylogenetic aspect of

sleep-dependent learning came also in the focus of research. Early life sensory deprivation in animals reduces sleep slow wave activity [36].

So, recent studies have shown that procedures presumably leading to local plastic changes in the cerebral cortex can result in local changes in slow wave activity during subsequent sleep, or in other words, the homeostatic process is use dependent and related essentially to cognitive activity.

The association of slow waves with cognitive processes is supported by the sleep findings in clinical disorders with mental decline. In normal senescence, parallel with the decay of mental activity, the sleep delta activity and the amount of delta rebound after sleep deprivation decreases [37]. Disorders damaging frontal lobes with consequent mental decline show in the same time sleep delta reduction. Alzheimer's disease and chronic alcoholism are good examples for this [38]. The same situation is detectable in sleep apnoea where apnoeic periods do not allow the development of delta sleep; consequently, cognitive functionsmay show important impair reflected by hypoperfusion of frontal lobes [39]. Chronic insomnia with deficient sleep delta activity also may impair cognitive functions [40, 41].

After summing up the most relevant new aspects of sleep research in the next chapters we will apply this knowledge to obtain new view points to understand more precisely the activation effect of NREM sleep in epilepsies.

Epileptic Networks. During the last 5–10 years due to several new data, a slow but decisive change seems to be developing in thinking about "generalized" and "focal" epilepsies. These research data clearly show that "generalized" epilepsies are not really generalized and "focal" epilepsies are not focal. Therefore the classical dichotomy of partial and generalized epilepsy became more and more meaningless, giving place to a unifying network concept. The so-called "generalized" epilepsies involve a bilaterally represented large cerebral system related to wide cortical association areas, namely, the thalamocortical system. "Focal" epilepsies are also not strictly localized to a geometrical "focus" but involve more or less wide sometimes bilateral (e.g. temporal and occipital epilepsies) regional circuitries. Concerning this kind of "network epilepsies"—although the seizure onset might origin consequently from one or more relatively restricted areas—the whole mechanism is more complex and determined by several influences and interrelationships, involving and transforming (in early onset) the functioning of physiological systems. Idiopathic epilepsies are embedded in functional systems of the brain and our knowledge about epilepsy is always dependent on the actual level of understanding in neuroscience, especially in neurophysiology.

The development of cognitive neuroscience led us to understand better the working modes in the higher order cortical areas [42–46].

Research of the last decade showed that all the mental processing serving cognitive functions, from simple to sophisticated ones, and the elaboration is executed instead of serial (sequential) processing by the strategy of "parallel distributed processing" [47].

Each module taking part of processing may serve in a flexible way different functional assemblies switching their composition according to the computational demand. The modules have no singular importance; only the pattern of cooperation among them is decisive.

Hierarchical features between brain areas are not able to explain the complexity and speed of binding the cerebral players to each other in cognitive functioning. Beyond hierarchy and connectivity (spatial dimension) another mechanism (in the time dimension, by temporal synchrony) recognized only at the middle of the nineties became the main candidate to explain binding. This temporal synchrony seems to work through synchronization of cerebral rhythms, especially by gamma oscillations.

Several lines of evidence demonstrated the appearance of gamma oscillation when higher elaboration was evoked by a sensory stimulus and when a cognitive task was processed. These findings provided lines of evidence for local oscillatory ensembles related to gnostic and cognitive elaboration in the cortex. A second step was to reveal that neuron ensembles apart from each other and even across to cerebral hemispheres come together in time transiently by gamma-frequency synchronization. This was evidenced firstly in the visual system [48] but later turned to be general principle working in several systems [49].

These above summarized features (parallel processing and binding by synchrony in gamma frequencies) delineate the working mode of physiological networks determining higher order processing in the brain.

Due to the multifold aspects revealed by the contemporary neuroimaging, neuropsychological, quantitative EEG (Q-EEG), and other sophisticated approaches of epilepsies, even when we can point out a certain area the resection of which renders the patient seizure free, nowadays it became clear that epileptic disorders reside not only in certain cortical spots or within geometrical mensuration but also extend in a more wider network.

The most important argument in favour of the network oriented view comes from the nature of epilepsy itself. It resides in preformed physiologically meaningful structures, with complex special situation, and possesses remote influences. Furthermore just because the characteristic increased level of excitability, it is very sensitive to triggering inputs. So epilepsy should be conceptualized in a more extended network than the seizure onset zone to which the surgery oriented approach mainly attached.

Nowadays we got more and more lines of evidence that epilepsy along with the physiological interconnections oversteps the artificial procrustean bed of anatomical lobes [50–52]. This is also an argument for conceptualizing epilepsies related to physiological networks instead of anatomical localizations.

The strict localization-related epilepsy concept has also a major drawback. The so-called generalized epilepsies are not fitting into it. Since more and more lines of evidence support the view that idiopathic generalized epilepsies are not really generalized and their characteristics are explained by the epileptic disorder of the thalamocortical system, using the working mode of the system in NREM sleep, this kind of

epilepsy has its explanation also in a physiological network turned to become epileptic (system epilepsies).

Neuronal networks in the cortex generate several distinct oscillatory bands, covering frequencies from <0.05 Hz to >500 Hz. Oscillators of different bands couple with shifting phases and give rise to a state of perpetual fluctuation between unstable and transient stable phase synchrony. The resulting interference dynamics are a fundamental feature of the global temporal organization of the cerebral cortex.

Collective behaviour of neurons is established through synchrony. Events that can be integrated over time by the target neurons are synchronous. Oscillatory coalition of neurons to form population synchrony may have a time window from hundreds of milliseconds to many seconds. Neuron assemblies are formed as transient coalitions with mutual interaction of discharging neurons [53].

Extension of EEG records to the high frequency oscillation (HFO) range revealed new vistas in epilepsy-related electrical activity and also shed more light to the properties of epileptic networks [54].

Two types of HFO have been distinguished: (a) ripples (R) with slower frequency (80–160 Hz) as physiological activity and (b) fast ripples (FR) with higher frequency (200–500 Hz) as a pathological activity, associated with epilepsy, described in experimental epilepsy models and in epileptic patients both with mesiotemporal and cortical epilepsies [55–57]. Concerning interictal HFO, the majority of them were associated with epileptiform sharp waves in time with the spike and not with the after-coming slow wave [58–60]. Interestingly HFO activity is maximal during slow wave sleep (up states) [61–64].

A manipulation that decreases HFO reduces the likelihood of seizures [65]. Increased FR ratio correlates with hippocampal cell loss and synaptic reorganization in temporal lobe epilepsy [63].

It seems to participate in epileptogenesis, being present already during the "silent period." A manipulation that decreases HFO reduces the likelihood of seizures. Therefore HFO and especially FR seem to be an essential player in epileptogenesis and in the electrographic phenomenology of epilepsies; furthermore it opens new diagnostic possibilities concerning the epileptic networks.

New spike and seizure functional MRI (fMRI) data mapping the irritative and seizure network in epilepsy provides a new functional anatomy of epileptic networks.

The systematic studies of Gotman and coworkers in MNI from 2003 and others [66–73] detecting epileptiform discharges and seizures by fMRI have led to several very important conclusions. They showed that spike discharges are related to either local blood oxygenisation level dependent (BOLD) positive or remote BOLD-positive/BOLD-negative signals. Even one spike may induce, beside local activation, remote consequences either in terms of excitation or depression of functions.

Generalized spike and wave type discharges show thalamic BOLD positive and diffuse cortical mixed signal with predominance of BOLD negativity. "Similarly" secondary bilateral "synchrony" type discharges show important diffuse cortical BOLD-negative components. Thus BOLD activation might make the network structure of irritative activity in the epileptic brain measurable.

Ictal studies were possible only limitedly due to movement artifacts when movements are prominent. However, when possible, BOLD activity may show in a noninvasive way the seizure pacemaker zone and the propagation network as well. These studies clearly proved that interictal and ictal discharges have much more widespread influence on brain functions than we conceptualized before. What is more, the exerted remote effect of spike and seizure activity is organized into complex activation/deactivation patterns that should be still more understood and probably will contribute to new functional anatomy epileptic networks.

Recently with group analyses of the individual interictal BOLD changes in different types (temporal and frontal lobe and posterior quadrant epilepsies) of epilepsy, Fahoum et al. [74] from the Gotman group were able to demonstrate common metabolic changes characteristic for the group that may not be apparent in images of the individual patients. For example, in temporal lobe epileptic (TLE) patients the largest activation cluster was in the cingulate gyri (ipsi- and contralateral), and the second cluster by volume included the insula, amygdala, and anterior hippocampus ipsilateral to the focus.

The positive BOLD activation was joined by common negative BOLD activation in the contralateral inferior parietal lobule and bilaterally in the posterior cingulum and precuneus (mostly in default mode network (DMN) structures). In patients with frontal lobe epilepsy (FLE) group analysis resulted in BOLD positive activation in the bilateral cingulum, contralateral cerebellum, ipsilateral frontal operculum, medial thalamus, genu, and posterior limb of the internal capsule.

Thus they confirmed that interictal discharges recorded from the scalp EEG may represent only a fraction of broader events that involve widespread brain areas despite their focal appearance. The group analyses proved that unique interictal networks can be related to different types of partial epilepsies.

Based on these studies we can assume that certain networks characteristic to the epilepsy type are under special "discharge load" with probable altering of the function of the involved structures, even during interictal periods without seizures.

Sleep Activation in Different Epileptic Networks

Thalamocortical Epileptic Network Underlying the Electroclinical Phenomenology of Epilepsies Hitherto Classified as Idiopathic Generalized Epilepsy (IGE). Under this heading, different groups of epilepsies are classified. The common clinical features are absences, multilocular myoclonic jerks, or generalized tonic-clonic seizures appearing with characteristic age dependency and the lack of initial focal symptoms (however thre are different lines of evidence for the frontal seizure origin both in experimental works [75] in clinical case histories).

From a syndromatological point of view, the following types were delineated: (1) childhood absence epilepsy (CAE), (2) juvenile absence epilepsy (JAE), (3) myoclonic absence

epilepsy (MAE), (4) eyelid myoclonia with absences (EMA), (5) perioral myoclonies with absences (PMAE), (6) juvenile myoclonic epilepsy (JME) with jerks without loss of consciousness and generalized tonic-clonic seizures (GTC) seizures, and (7) IGE with awakening GTC seizures (EGMA).

The EEG shows in interictal state certain variations of bilateral frontal dominant spike and wave discharges. Ictal EEG pattern is bilateral extended spike-wave discharges (absence), multiple spikes and waves (myoclonic seizures of JME), and repetitive spiking in the tonic, then slowing down to packages of spike-waves and alternating with suppressed periods (generalized tonic-clonic seizures).

We have evidence, provided by several studies, where during interictal spike-wave discharges a transient cognitive impairment (TCI) is detectable [76].

Neuroimaging did not show structural cerebral alterations studied by routine protocols, however in JME patients frontomedial structural changes were demonstrated by histological [77] and by MRI morphometric methods [78]. The disorder has an inheritance probably caused by a variation of multigenetic constellations not yet thoroughly revealed with separate endophenotypic characteristics of the seizure, EEG, and other features (like photosensitivity).

The working mode of the system by which the spike pattern develops is proved to be the same that works during NREM sleep opposed to waking and REM state (see in the previous chapter in more details). This working mode is characterized by "burst firing" when both cortical and thalamic neurons produce excitation alternating with inhibition or disfacilitation in high synchrony. The pacemaker of inhibition executed on the thalamic relay cells is the thalamic reticular neurons. Electrophysiological studies revealed a very complex thalamocortical circuitry with multiple transmitters and special membrane properties involving cortical pyramidal, thalamic relay, and thalamic reticular neurons producing intermittent recurrent excitation and inhibition behind the characteristic bilateral spike-wave pattern.

Relationship between NREM Sleep and IGE Symptoms. There is a close relationship between vigilance level and expression of spike-wave paroxysms. Spontaneous paroxysms are promoted by transitory decreases of vigilance level during awake state[79, 80], after awakening, after lunch, in evening sleepiness, during boring tasks or situations, experimental depression of reticular arousal functions [81], and after sleep deprivation. Spontaneous paroxysms are inhibited by a sudden increase in vigilance [82, 83], arousals (calling by name), and experimental stimulation of the reticular arousal system. This relationship stems from the common "burst firing" working mode of the thalamocortical system sharing by a mechanism that sets into motion both in shifts toward slow wave sleep and in spike-wave pattern.

However, the fact that spike-wave activation in the form of absence-like 3 Hz paroxysms occurs selectively in transitional periods (between slow waves sleep and wakefulness and between slow wave and REM sleep) and that spike-wave pattern is absent in REM sleep both in humans [78, 79, 84–86] (Figure 4) and animals [87, 88] and is present only in distorted groups during deep slow wave sleep needs explanation. Studies analyzing this relationship have shown that not only the level of vigilance differs but activation in these transitional periods is closely connected with sudden oscillations of vigilance attached to the so-called phasic events of sleep. Spontaneous paroxysms (with or without clinical manifestations) have been associated with arousal-dependent phasic events preceded by K-complexes and/or slow waves [89, 90]. With sensory stimulation these dynamic changes could have been experimentally elicited and studied [90]. Association of generalized spike-wave pattern in IGE with sleep instability in NREM sleep can be measured by the CAP phenomenon, the frequency of which is proportional with sleep instability. Sleep EEG analysis of primary generalized patients [91] showed significant prevalence of spike-wave paroxysms during CAP as compared to NCAP periods (68% versus 32%), 93% of all the spike-wave patterns occurred in CAP were found in the reactive phase A. In sleep EEG analysis of JME patients [92] spiking rate was significantly higher in CAP A phase compared to NCAP and showed strong inhibition in CAP B phase. The link between EEG microarousal phenomena and spike-wave paroxysms is in apparent contradiction to the association of spike-wave pattern and sleep-like bursting mode of the thalamocortical system. To solve this contradiction we should take into consideration that most of the evoked phasic events during the dominance of the bursting mode show the features of sleep response. They contain clear-cut synchronisational slow wave sleep elements (single or serial K-complexes, slow wave groups) occurring in the same form as in the spontaneously appearing counterparts. Each phasic activation during slow wave sleep seems to evoke a regulatory rebound shift toward sleep, which seems to be the best activator of the oscillatory mode of thalamocortical network and the spike-wave mechanisms as well [84, 90].

There is another aspect in which NREM sleep and absence seizures share important features, namely, the global decrease of cortical activity during both absences and NREM sleep. Absences with 3 Hz synchronized spike-wave pattern are composed by two distinct components. The underlying events during the "spike" component proved to be unequivocally a pronounced glutamatergic burst discharge both in cortical and thalamic relay cells. The "wave" component was previously viewed as summated inhibitory postsynaptic potentials attributed to GABA-ergic inhibitory process in pyramidal cortical neurons. Later Steriade [20] showed that instead of inhibition a "disfacilitation" (decreased neural activity) is present during the "wave" component.

Transcranial doppler (TCD) and single photon emission computed tomography (SPECT) studies in experimental animals [93, 94] and in humans [95] showed cortical decrease and thalamic increase of blood flow during absences. On functional magnetic resonance imaging (fMRI) studies thalamic structures showed positive BOLD activation, while over wide cortical fields patchy negative BOLD activation has been observed [66].

Similar features proved to be true for NREM slow oscillation (as it was described in the first part). Steriade et al. [14] discovered that beside delta activity a slower oscillation (<1 Hz, generally 0.5–1.0 Hz) exists, and this slow oscillation

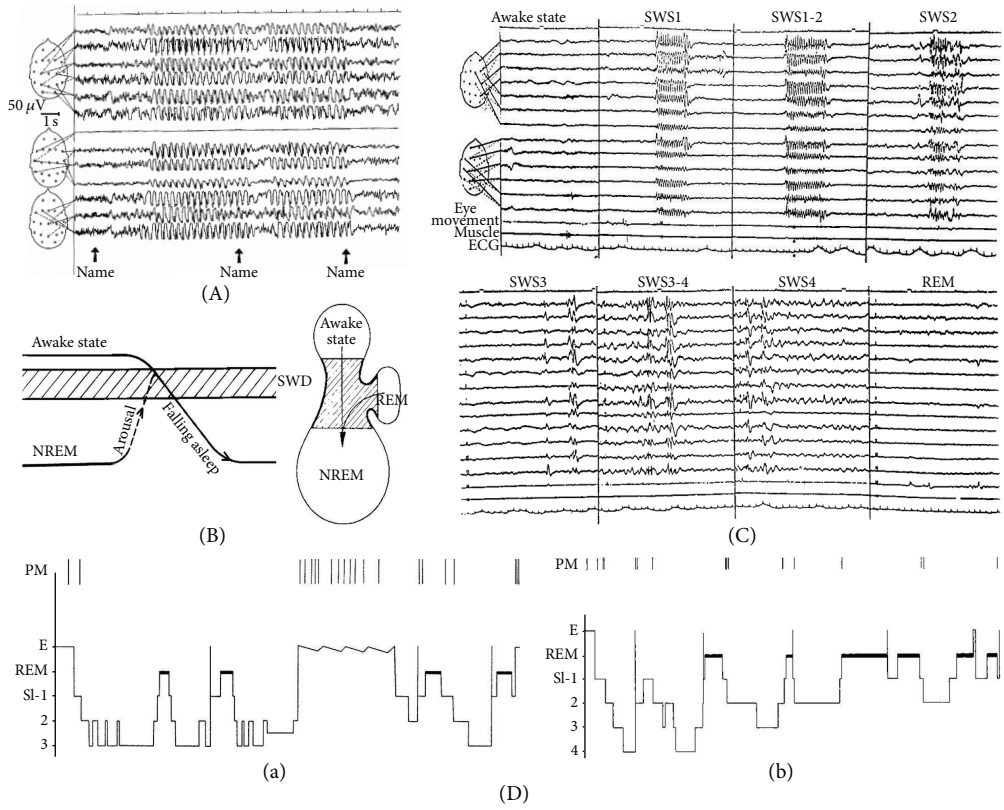


Figure 4: Composite figure demonstrating the association of ictal type of spike-wave paroxysms with transitory periods between awake and NREM sleep. (A) shows that absences with generalized spike-wave pattern can be elicited by arousing stimulus (calling by name), while the same arousal blocks the pattern by increasing level of vigilance. (B) Schema of the optimal level for absences reachable either by arousal from light sleep or falling asleep. (C) and (D) The distribution of spike-wave activity across the sleep stages. Absence type ictal activation appears exclusively in the transitional periods between awake/NREM and REM/NREM sleep. Attentional awake state usually and REM sleep always block absences. (D) Distribution of absences (indicated by perpendicular lines) across sleep cycles in night sleep in absence epileptic patients.

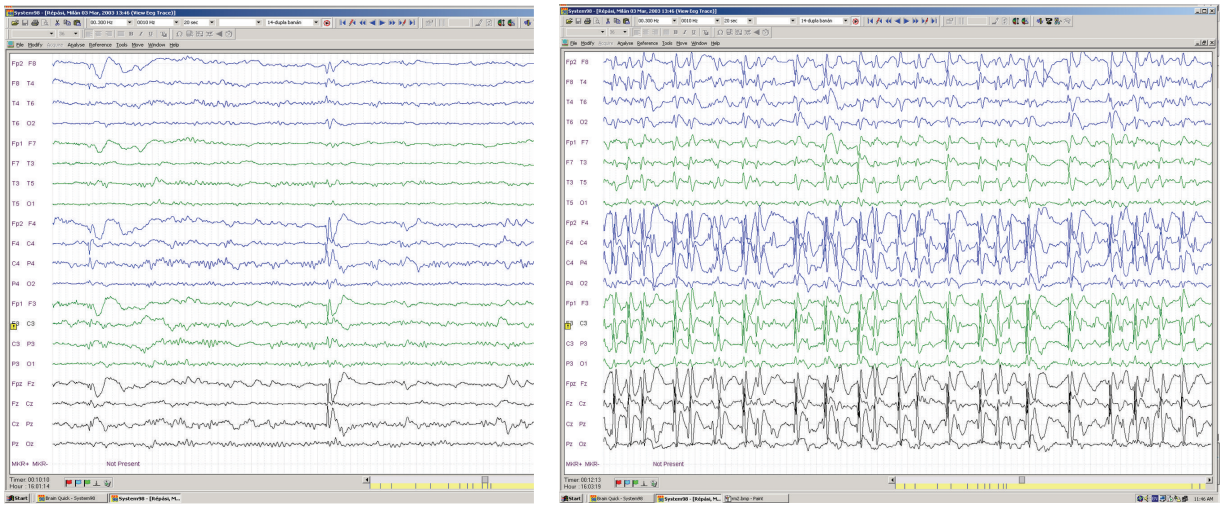
plays role in grouping of delta waves and spindles during deep NREM sleep, with mechanisms essentially cortical in origin. The slow oscillation consists of a prolonged depolarizing phase (up-state), followed by long-lasting hyperpolarization (down-state). The up-state shows dense excitatory and inhibitory synaptic activity, while the down-state is characterized by cessation of synaptic barrages (disfacilitation). The Steriade group provided ample evidence that slow oscillation involves the cortex widely, opposed to faster oscillations originating in more restricted circuits.

NREM and IGE Absences Share Common Physiological Circuits. Both in deep NREM sleep and in absences the cortical activity is reduced in certain (mainly frontal) areas. In absence the loss of contact with the outer world may have a twofold reason, because (1) the bursting mode interrupts the continuous flow of information from our surrounding to the cortex, (2) the disfacilitation during the "wave" component involving the cortical association areas decreases the possibilities of cortical elaboration. The sensory information flow is impaired in both conditions. Sensory stimuli have an awakening effect in sleep and a disruptive effect in absence seizures too. Sleep induction promotes absences and awakening inhibits both sleep and absences.

So the functional neuroimaging, neurophysiologic, and clinical data became recently highly congruent, pointing to the thalamocortical network as a common substrate of NREM sleep and IGE. Therefore the slogan of Steriade: "sleep and epilepsy are bedfellows" is really very witty here. Spike-wave discharges of IGE represent the epileptic exaggeration of the bursting mode of the thalamocortical system. Therefore the inducement or shift toward NREM sleep promotes the manifestations of IGE. The well-known activating effect of sleep deprivation and sleep per se is probably related to the same mechanism [96].

Since the thalamocortical system can be influenced by other cortical and brain stem systems the epileptic disorder may originate from several routes (e.g., as gen-related channelopathies). As yet we do not know which one is realized in the human phenotypes. Several experimental and genetic models exist demonstrating this multiplicity by which the same system can be activated.

Idiopathic Focal Childhood Epilepsies (IFCE), Landau-Kleffner Syndrome (LKS), and Electrical Status Epilepticus in Sleep (ESES) Continuum. Within this spectrum of epileptic disorders the first group, namely, the IFCE itself, consists of a spectrum to which all the idiopathic focal childhood



Young patient with atypical features of rolandic epilepsy wake state

(a)

The same patient during NREM sleep: "focal status electricus during sleep"

(b)

Figure 5: Rolandic epilepsy with atypical features: progressive cognitive impairment and focal status epilepticus like activation of interictal discharges during NREM sleep.

epilepsies belong. Nowadays we see Idiopathic Focal Childhood Epilepsies as a spectrum of epileptic disorders being the most frequent, genetically based nonlesional epilepsy in childhood [97]. However, the clinical boundaries of the syndromes, which belong to this spectrum, are still in evolvement, the following diagnostic criteria seem to be already solid: (a) normal neurological examinations, (b) normal intelligence, (c) normal neuroimaging, (d) family history of seizures, especially benign types, (e) monotypic seizures, stereotyped in clinical manifestation, (f) frequent occurrence in sleep, (g) seizures are easily controlled with antiepileptic drugs, and (h) beginning age determined, with onset rarely before 3 years or after the age of 16-17 years and with spontaneous, age-dependent resolution, principal EEG features include normal background activity, spikes with characteristic morphology and localization, resembling to focal spike-wave discharge, activation during sleep, and in a part of patients generalized SWD.

There is a large diversity in the topography of spikes. Patients with benign focal epileptiform discharges (BFED) frequently have bilateral-independent or bilateral synchronous discharges. The spikes in idiopathic centrotemporal epilepsy (ICTE) may be ipsi- or contralateral to the symptomatogenic side. Furthermore, BFED are frequently multifocal. The most frequent combinations are bilateral-independent or synchronous centrotemporal or occipital discharges. The centro-temporal and occipital spikes are also frequently seen in combination, and some patients have more than two spike foci in a recording.

All these observations tend to change the concept of focal epilepsy towards a more widespread genetically based condition of increased cortical excitation with shifting predominance. The epileptic dysfunction is not localized to a circumscribed small area, but it is imbedded in a broader network of the associative cortex. Probably the most relevant approach is the concept of Doose et al. [98] stressed also by Panayiotopoulos et al. [99], who assumed behind these floating features a "seizure susceptibility disorder" related to certain "hereditary maturational impairment."

In the last years the most frequent form of IFCE, Rolandic epilepsy with centro-temporal spikes turned to be less "benign" as it was assumed before [100, 101], and the described so-called "atypical" variants paved the way to find the continuum between them and LKS and ESES. Nowadays we seeseveral variations of patients seemingly belonging to the focal benign childhood epilepsies. These patients show in awake state focal interictal discharges, but they may have abundant serial focal (pseudogeneralized) discharges, not rarely focal status electricus in NREM sleep and have more cognitive impairment during their long-term course (Figure 5).

LKS is a childhood disorder occurring in previously normal children, characterized by the loss of language skills, acquired verbal auditory agnosia, multifocal spikes, and spike-wave discharges mainly localized over the centrotemporal regions, continuously or subcontinuously during sleep. Epileptic seizures (usually rare), behavioural disorders, and hyperkinesias are observed in about two-thirds of patients. "The prognosis is favourable, with remission of seizures and EEG abnormalities before the age of 15 years" [102]. No evidence of associated focal brain lesions has been documented. Deonna and Roulet-Perez [103] in their recent review emphasized that "Landau-Kleffner is now seen as the rare and severe end of a spectrum of cognitive-behavioural symptoms that can be seen in idiopathic (genetic) focal epilepsies of childhood, the benign end being the more frequent typical rolandic epilepsy."

At the early stage of the disorder unilateral IEDs are more common, resembling discharges seen in IFCEs, localised to a wide area around the Sylvian fissure. Bilateral "generalized" SW is also common. Later bilateral focal discharges are prevalent in roughly homologous areas.

ESES is a rare condition characterised by the coexistence of the following aspects: (1) ESES pattern in NREM sleep occurring in at least 85% of NREM sleep and persisting on three or more records over a period of at least one month; (2) cognitive impairment, in the form of global or selective regression of cognitive functions; (3) motor impairment (ataxia, dyspraxia dystonia, or unilateral pyramidal deficit); (4) rare epileptic seizures (particularly in the period of ESES) with focal and/or generalised seizures (uni- or bilateral clonic, GTC, and complex partial seizures or epileptic falls tonic seizures never occur). The EEG abnormalities disappear around puberty, and the epilepsy shows a benign outcome too, but the cognitive impairment is not completely reversible in all cases, and some residual impairment remains. LKS and ESES are separate entities, but the two conditions show a wide overlap.

These epilepsies are characterized by the abundance of regional epileptiform discharges in sharp contrast with the rare and in several cases lacking seizures. The nature and severity of interictal cognitive symptoms are closely related to localization within the network and amount of epileptic interictal discharges.

In this spectrum disorder activation in sleep has a special significance.

In IFCE NREM sleep characteristically increases the occurrence rate, amplitude, and distribution field of interictal epileptiform discharges(IEDs) [104]. Some studies found that "maximum spike/min ratios were related to slow sleep stages, especially delta sleep, and in general to the first cycle" [105]. A relationship between spikes and spindle sleep had been shown long ago [97, 106, 107].

In LKS NREM sleep has a strong activating effect. The transition from LKS to ESES during long-term clinical and EEG followup has been described [108–110]. Usually REM shows no discharges, and in all cases described no generalized GSW were present during REM sleep. Methohexital studies performed by Ford et al. [111] showed that one hemisphere is "driving" the other in bilateral discharges.

In ESES the NREM sleep activation is the most characteristic feature, in the form of GSW 1.5–2 Hz discharges presenting continuously across all sleep stages, beginning immediately with the start of NREM sleep [112]. The pattern of cognitive impairment may differ from patient to patient; the proportion of speech dysfunction is also variable and the type of impairment seems to depend on the localisation of the field exhibiting generalized spike-wave (GSW) discharges [113–116]. There is a close temporal relationship between ESES and the neuropsychological deterioration and parallels between the duration of ESES and the neuropsychological outcome. ESES is a kind of status epilepticus leading to nonconvulsive seizure symptoms hidden in sleep, manifested repeatedly during sleep, causing prolonged interference with cognitive functions [115], Recently it was shown by Tassinari et al. [116] that slow wave downscaling measuring according to amount of SWA, amplitude of slow waves, slope of waves, and amount of multipeak waves during night sleep is impaired in ESES patients.

All three syndromes are characterized by a transient, age-dependent, nonlesional, and genetically based epileptogenic abnormality (however ESES may develop on the basis of structural damage as well). The brain tissue responsible for the disorder is localised around the Sylvian fissure and strongly correlated with speech function and cognition [117]. The interictal discharges are partially localized to this perisylvian area and partially show different degrees of generalization and secondary bilateral synchrony. Discharges in all syndromes appear in the form of a focal or generalized spike-wave pattern. The amount and persistence time of interictal discharges seem to correlate with the degree of cognitive deficits, and there is a correlation between the degree of spiking during sleep and the degree of cognitive deficits across syndromes.

The epileptic discharges are accompanied with a slow wave component, associated with cognitive deficits rather than frequent seizures. This characteristic situation has been called "cognitive epilepsy." The slow wave components of the GSW discharges may protect against conventional sustained, depolarization-based seizures but on the other hand interfere with normal cortical functioning. This assumption is strongly supported by several new results showing that sleep has a use-dependent homeostatic function, connected with sleep slow wave activity, needed for the plastic functions and impaired when abundant epileptic discharges interfere with it [118, 119].

Lennox-Gastaut Syndrome (LGS) as a Developmental Epilepsy with Early Involvement of the Corticothalamic System. LGS is an age-dependent syndrome beginning before the age of 4, but the termination is not clear. Patients may have a persistent syndrome during adulthood; there may be a "late onset LGS" as well [120–123]. The coexistence of several seizure types is typical. The most characteristic are tonic axial seizures occurring more frequently during NREM sleep, causing drop attacks in the wake state. Atypical absence with irregular GSW paroxysms is the other characteristic seizure form. The EEG shows frequent slow spike-wave paroxysms emerging from a slow and irregular background. Mental retardation is the rule. LGS is assumed to develop through "secondary generalization" based on early involvement of the thalamocortical network [124]. One of the most important features of LGS is that interictal and ictal epileptic manifestations appear during brain development suggesting that "excitation-producing etiologies and/or genetically induced aberrant cortical development and physiology during a sensitive window of enhanced epileptogenicity in the immature central nervous system induce synaptic remodelling leading to homotopic and thalamic epileptic discharge propagation and a diffuse bisynchronous epileptogenic process, with excess cortical excitation and increased corticothalamic oscillation" [124].

NREM sleep importantly activates slow GSWs, but their frequency does not reach the level seen in ESES. Another very characteristic feature of NREM sleep in LGS is the presence of runs of generalized paroxysmal fast activity (GPFA).

The appearance of GPFA shows a strong correlation with deep slow wave sleep. These runs are bilaterally synchronous, with frontal predominance; their frequency is around 10 Hz. Very frequent in NREM, they never occur in REM and are rare in waking. Polygraphic recording reveals some ictal involvement in most of them. The most regularly observed somatic concomitant of the discharge is acceleration or deceleration of the heart- and respiration rate and increase of axial tone, most conspicuously in the neck muscles with a small elevation of the head and a little opening of the eye lids.

The slow GSW activity so characteristic for LGS has a frontal predominance and belongs to the category of secondary bilateral synchrony [125, 126]. This kind of pattern is held to be the result of focal epileptic activity propagating to the contralateral hemisphere through the corpus callosum, driving widespread corticothalamic entrainment [126].

The frequent occurrence of GPFA and their morphology raises the possibility of a relationship with sleep spindles. There is a relationship between the presence of slow spike wave discharges and GPFA. In our material the association of GSWD and GPFA was more than 90% in either ictal or interictal states.

In Doose syndrome where GPFA is not present, mental deterioration is less frequent and not as severe as in LGS [127, 128]. Recently we reported exceptional cases where typical paroxysmal fast activity was present without mental deterioration and intractability in difficult to treat IGE patients [129].

The influence of the frequent discharges mainly in sleep might have an effect on mental development. A possible effect could be interference with memory consolidation during NREM sleep [130]. Distorsion of physiological spindling by GPFA leading to giant pathological spindles may have a special worsening effect on memory consolidation.

Earlier we worked out a concept interpreting GPFA as a final common pathway of malignization concept for primary and secondary generalized epilepsies [125] (Figure 6). Observing the paradoxical GPFA eliciting acute effect of benzodiazepine drugs and barbiturates we assumed an iatrogenic transformation of the GABA-chloride ionophor complex receptor structure by chronic use of these drugs in the treatment of these patients. The clinical impression that in the last 5–10 years the occurrence of GFPA is decreasing would support the hypothesis.

Epilepsy with Unilateral or Bilateral Involvement of the Temporolimbic Network. Temporolimbic network epilepsy (TLNE) is the most frequent epilepsy type in adulthood [131, 132]. The most frequent etiology is hippocampal sclerosis (HS) preceded by an "initial precipitatory insult" (atypical febrile seizure or status epilepticus) damaging the hippocampus and initiating an epileptogenic synaptic reorganisation in this structure, which may only lead to epilepsy after a long period (Mathern et al. 1996). Synaptic reorganisation of the hippocampal network is a key point in the evolution of temporolimbic epilepsies [133–135]. Other frequent etiological factors are tumours (gangliogliomas, embrioplastic neuroepitheliomas, and oligodendrogliomas), cortical dysgenetic malformations, cavernomas, and posttraumatic and postencephalitic lesions.

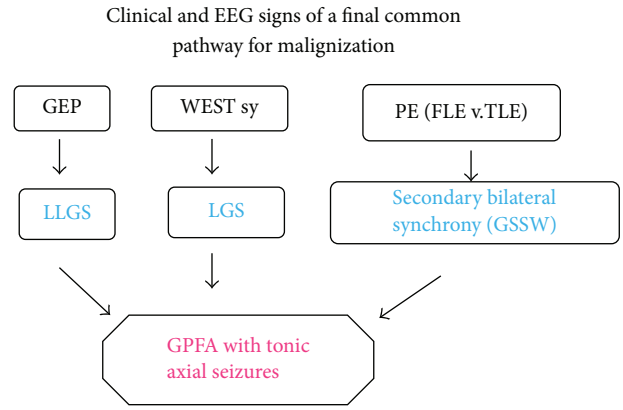


Figure 6: Schema of clinical and EEG signs of a final common pathway of malignization in three groups of patients: (1) West syndrome, (2) idiopathic generalized epilepsy, (3) certain frontal and temporal lobe partial epilepsies through secondary "Lennoxisation," showing generalized fast paroxysmal activity usually in NREM sleep.

The main substrate of TLNE is held to be the hippocampus; however, more widespread temporal structural damage apparently plays a role [136, 137]. In the majority of temporolimbic epilepsies (TLNE) interictal EEG (mainly during sleep) or other diagnostic categories (neuropsychology, MRI, FDG-PET, MR spectroscopy, pathological work up) shows bilateral involvement and frequent contralateral spread of seizures.

Complex partial and secondarily generalized seizures originating from the TLNE are frequently apparent during sleep as well as waking. Sleep seizures are more frequent in NREM sleep, and secondarily generalized seizures tend to be more prominent in sleep. Discharges in sleep appear in higher rate and in a more explicit form compared to the wake state findings. NREM sleep is associated with an increase of spiking rate, extension of electrical field, and the rate of bilateral independent discharges, while in REM sleep a restriction of the electrical field was observed [138–141]. Within NREM sleep the activation of temporal spiking was found to be the highest in stages 3-4 [139] increasing as patients move to deeper stages of NREM sleep [142]. Temporomesial compared to temporolateral cortical structures may display spiking at different sleep levels [143].

A small number of patients show activation during REM sleep, localizing the primary epileptogenic focus better than spike activity in either waking or NREM sleep.

Medial temporal lobe epilepsy has been conceptualized more and more as a spectrum of conditions showing a continuum between unilateral and bilateral involvement (Figure 7). Whether this continuum reflects a progressive course (secondary bilateralization) or determined purely by etiological constellations is still not enough clarified. The propensity to express bilateral discharges is particularly reflected in sleep records. The persistence of bilateral-independent interictal spiking in NREM sleep after surgery proved to be strongly associated with bad surgical outcome in our study [144].

The characteristic cognitive deficit conjoining TLNE is disturbance in declarative memory, due to hippocampal

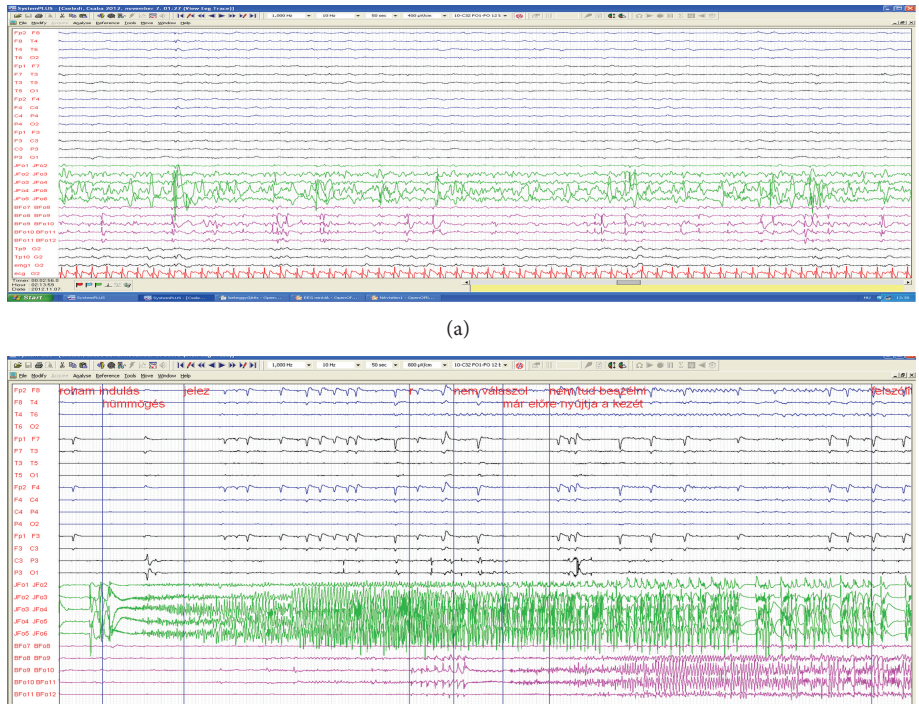


Figure 7: Interictal (a) and ictal (b) record of a patient with mediotemporal epilepsy investigated with foramen ovale (FO) electrodes picking up mediotemporal activity. (a) Intensive spiking in both FO electrodes independently with separate electromorphology, with abundance of slow waves in the right FO (green). Spiking is only sparsly reflected in the scalp electrodes. (b) Ictal recording shows seizure start that simultaneously with the clinical onset as sigma range oscillations in the right FO electrode contacts. Propagation to the contralateral side (purple) was seen several seconds later. Scalp electrodes show ictal activity only after propagation to the contralateral side in the FO, with theta range rhystmic activity. This record demonstrates the difficulties to verify the laterality relations in mediotemporal epilepsies without intracranial recordings, when both sides are involved.

dysfunction which is in a certain extent side specific related to verbal memory in the dominant side and to visuospatial memory in subdominant hippocampal impairment.

The role of hippocampus in memory consolidation in a dialogue with the cortex during NREM sleep, proposed firstly by Buzsáki [145], seems to be more and more studied in details and supported also in human beings [146–149]. It is plausible to assume that the memory impairment related to NTLE is underpinned by the epileptic interference with this process by hippocampal discharges, but direct proof of this is still lacking. There are only some lines of evidence for the role of epileptiform discharges during NREM sleep in the memory deficit interfering with hippocampal-cortical dialog [149].

Nocturnal Frontal Lobe Epilepsy (NFLE) and the Prefrontal Mediobasal Network. Since the early 1980s, a series of studies reported on patients with peculiar short motor seizures and dystonic-dyskinetic features, usually involving both sides of the body, clustering during NREM sleep, often accompanied with strange vocalisation, under different headings [150–152]. The attacks recur (with multiple episodes during the night) almost every night, at least in certain periods of the course of the disease. Consciousness is preserved or regained very soon. Approximately one-third of patients exhibit some kind of interictal epileptiform discharges (IED) localised to the frontal region. Ictal scalp EEG recording reveals epileptic features only exceptionally. The motor pattern is highly stereotyped for each individual with slight variation but may have highly variable patterns across patients. Almost half of the patients exhibit occasional GTCs in waking or sleep.

The seizures vary in the character of the hypermotor pattern. In some seizures the asymmetric tonic postural component is more prominent resembling those originating from the supplementary sensory-motor area (SSMA) region. The higher occurrence rate of SSMA seizure in sleep compared to wakefulness was demonstrated by Anan and Dudley [153].

In the mid 1990s Scheffer and coworkers [151] described a familial variant of NFLE with autosomal dominant inheritance (ADNFLE).

Beside the association of NFLE seizures with sleep, there is also a characteristic link with NREM arousal dynamics. Seizures are always preceded by micro-arousals. Terzano et al. [154] demonstrated that motor events are closely related to periods of unstable NREM sleep and began during a CAP *A* phase. The overall CAP rate in his patients was increased, and when attacks were suppressed, the CAP rate decreased. In this kind of epilepsy the association of clinical (motor) epileptic events with NREM sleep arousal events is evident.

In ADNFLE an epileptic sensitisation of the cholinergic arousal system has been found [18, 155]. This is underlain by

ACh receptor mutations in different brain structures belonging to the arousal system [156]. The number of microarousals during NREM sleep increases in this type of epilepsy, and they release epileptic events [157]. Arousal disorder a kind of parasomnia in NREM sleep shows very similar symptoms both regarding the symptomatology of the nocturnal events and also regarding the interrelationship of the events with NREM micro-arousals. In addition there is a clear overlap in the occurrence of NFLE and arousal parasomnia within the patient's families [158].

We propose that pathological arousals accompanied by confused behavior with autonomic signs and/or hypermotor automatisms are expressions of the frontal cholinergic arousal function of different degree, during the condition of depressed cognition by frontodorsal functional loss in NREM sleep. This may happen either if the frontal cortical Ach receptors are mutated in ADNFLE (and probably also in geneticaly not proved nonlesional cases as well), or without epileptic disorder, in arousal parasomnia, assuming gain in receptor functions in both conditions.

Further we propose that NFLE and IGE represent epileptic disorders of the two antagonistic twin systems in the frontal lobe (Figure 8). NFLE is the epileptic facilitation of the ergotrop frontal arousal system, whereas absence of epilepsy is the epileptic facilitation of burst-firing working mode of the spindle and delta producing frontal thalamocortical throphotrop sleep system [159].

NFLE patients do not show much cognitive disturbances, neither ictally nor interictally. The lack of scalp EEG involvement is an interesting characteristic of NFLE, partially due to the localisation of epileptogenic areas in the hidden frontomedial and orbital surfaces. The interictal discharges do not show any GSW characteristics. This supports the assumption that the spike-wave generating thalamocortical system is not involved in NFLE. We have to assume that in NFLE arousal activation has direct access to frontal cortical circuitry involving the basal ganglia, responsible for hyperkinetic motor paroxysms. Greater involvement in motor functions contrasts with epilepsies related to the corticothalamic network, involved more in sensory information processing and cognition. Moreover a striking contrast can be established between the IGE and NFLE, while IGE may represent the epilepsy of the NREM sleep trophotrop network, the NFLE, and the ergotropic frontal cholinergic arousal/alarm network.

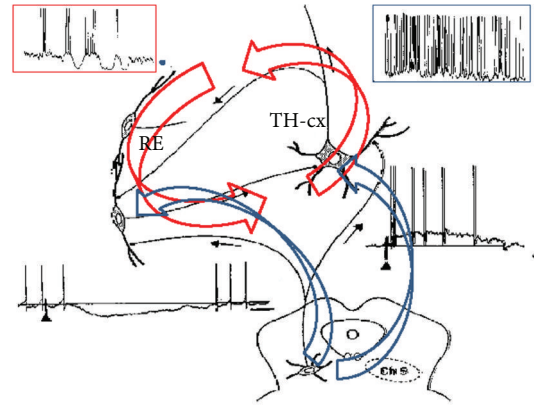


Figure 8: Schematic representation of arousal (blue) and sleep (red) network, according to Itier and Bertrand [18] using the Steriade's drowing [19]. In the inserts the thalamocortical transmitting mode is shown: in red frame the burst-firing mode during NREM sleep and in blue frame the tonic mode conveying continuous impulses from the thalamus to the cortex. The below other two inserts show how cholinergic arousal system inhibits the thalamic reticular activity which in the burst-firing mode provides recurrent inhibition of the thalamic relay neurons (big red arrow). The other influence of the arousal system fuels the cortical arousal through the thalamic relay cells.

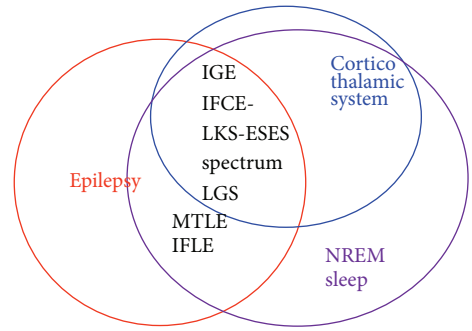


Figure 9: Relationship among the epilepsy networks, NREM sleep network, and the corticothalamic system.

2. Conclusions

Both clinical and EEG manifestations of many epilepsy syndromes linked to aspects of sleep and epileptic EEG manifestations in sleep are strongly associated with the presence of cognitive dysfunction (Figure 9).

It is clear that in epilepsies involving the corticothalamic network like in IGE, the perisylvian network or LGS are harmful for cognition. Interference with cognition seems to be parallel to the amount and extension of SW discharges in NREM sleep. Discharges originating from one part of the thalamocortical associative areas can interfere with functions represented in that part of the network. For example, in LKS discharges in the perisylvian, mainly posterior part of the first temporal convolution interferes with certain aspects of speech function [160]. A more extensive functional deficit may be related to cortical disfacilitatory effects of the wave component of GSW discharges demonstrated by electrophysiological [161] and fMR methods [65]. A third component of cognitive impairment may be the interference of GSW discharges with the increasingly evidenced restorative functions of NREM sleep [118]. Therefore nowadays we have more and more evidence supporting the view that NREM sleep, and especially delta sleep homeostatic regulation, is governed by use-dependent plastic processes. In other words delta homeostasis and use-dependent plasticity are two different sides of the same coin probably representing the biological function of slow wave sleep [119, 162].

The occupation of a considerable amount of slow wave sleep by spike-wave discharges as in ESES and LKS or even in a more circumscribed way by rolandic discharges, and also in LGS, obviously interferes with restorative function, resulting in exhaustion of cognitive capacities.

NFLE syndrome, without the entrainment of the SWD generator corticothalamic system, is relatively free from cognitive deficits that are in striking contrast with the well-known importance of the frontal lobe in cognitive functions.

In TLNE the development of secondary bilateral synchrony probably involves the thalamocortical system and may be responsible for certain cognitive decline, and the local involvement of hippocampal memory circuits interfere with the hippocampal dialog ensuring memory consolidation during sleep. In addition structural lesions due to the etiological factors (tumour, trauma, encephalitis, etc.) also may contribute to local cognitive dysfunctions.

Activation during sleep is related to the network properties of the particular epileptic syndromes. So we can differentiate between several types of epileptic network activation by sleep: (1) via the thalamocortical system as main route and (2) other ways like (a) frontal epilepsy by epileptic transformation of the cholinergic arousal system in NREM sleep, (b) activation of temporolimbic epilepsy by NREM and REM sleep via hippocampal changes during sleep.

Another aspect which has been mentioned during this work is that epileptic activation during NREM sleep is linked to phasic activation of reactive delta bouts. It is a global relationship with sleep valid for almost all epilepsies. In the majority of epilepsies interictal epileptiform discharges and also seizures are gated by CAP and within CAP A1 phase. In deep NREM sleep the up states of the bellow 1 Hz slow oscillation contain rich synaptic and HFO activity, while during down states disfacilitation is overwhelming. The alternation of these states with extremely opposite functionalities across alternations of up and down states might be also candidates to play important role in gating epileptiform activity.

Abbreviations

IGE: Idiopathic generalized epilepsy
IFCE: Idiopathic focal childhood epilepsies
LKS: Landau-Kleffner syndrome
ESES: Electrical status epilepticus in sleep
LGS: Lennox Gastaut syndrome
MTLE: Medial temporal lobe epilepsy
IFLE: Idiopathic frontal lobe epilepsy.

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Review Article

Epilepsy, Antiseizure Therapy, and Sleep Cycle Parameters

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A reciprocal relationship exists between sleep and epilepsy. The quality of sleep is affected by the presence and frequency of seizures, type of antiepileptic therapy utilized, and coexisting primary sleep disorders. Daytime somnolence is one of the most common adverse effects of antiepileptic therapy, with specific pharmacologic agents exhibiting a unique influence on components of sleep architecture. The newer generation of antiseizure drugs demonstrates improved sleep efficiency, greater stabilization of sleep architecture, prolongation of REM sleep duration, and increased quality of life measures. The emerging field of chronoepileptology explores the relationship between seizures and circadian rhythms, aiming for targeted use of antiseizure therapies to maximize therapeutic effects and minimize the adverse events experienced by the patients.

1. Introduction

Although the complex relationship between sleep and epilepsy has not been fully elucidated, it is well known that sleep disturbance provokes seizures and that seizure activity may influence the quality of sleep. In addition, antiepileptic drugs (AEDs) that are commonly used for seizure treatment affect sleep quality and architecture. Some AEDs tend to cause sleepiness or drowsiness while others can lead to insomnia. Sleep is an essential physiologic state that influences restorative and memory consolidating functions [1]. As previously recognized, the relationship between epilepsy and sleep disturbance is likely multifactorial: the direct effect of seizures, adverse events due to AED therapy, presence of psychiatric comorbidity, and coexisting sleep disorders all have the potential to contribute to alteration of sleep architecture and the subjective quality of sleep. Accordingly, one would expect that lack of sound sleep would significantly impact neurocognitive and psychological function, especially in patients treated with AEDs for their seizures. It is important for clinicians to understand the proclivity of a specific AED to affect the quality of sleep in order to guide epilepsy therapy and prevent disturbance of a patients' nocturnal recovery. This review systematically evaluates the currently available literature, elucidating the effect of antiepileptic drug therapy upon the sleep cycle. A search of relevant primary research and review articles was performed utilizing the PubMed database.

2. Epilepsy and Sleep

Sleep is classically divided into REM and non-REM phases as defined by the parameters of electroencephalography, respiration, eye movement, and electromyography. The non-REM phase consists of the light stages of sleep—N1 and N2 (previously designated stages 1 and 2), followed by deeper predominantly slow wave sleep (SWS)—N3 (previously divided into stages 3 and 4). Disturbance of sleep is consistently ranked among the top three adverse side effects in patients with epilepsy. Subjective sleep complaints in the prior 6 months were reported by up to 39% of patients with partial epilepsy as compared to 18% of controls [2]. The largest differences were observed in measures of excessive daytime sleepiness (13.8%) and psychiatric sleep disorder (14.1%). The authors concluded that sleep disturbance contributes to a lower quality of life independent of epilepsy diagnosis or its treatment. Sleep complaints in adult patients with epilepsy reported in other questionnaire-based studies varied from 16.9% to 36% [3].

Both NREM sleep and its deficit promote epileptiform discharges, with more profound effect on diffuse discharges. In contrast, during REM sleep, the topology, distribution, and

frequency of epileptiform discharges are decreased [4]. A number of authors attribute facilitation of epileptiform activity during NREM sleep to increased synchronization of the EEG pattern; in contrast, inhibition of epileptiform activity during REM sleep could be explained by desynchronization of cerebral networks [3].

Sleep efficiency is the time spent asleep divided by the time spent awake during a given sleep period. In normal subjects this value should be more than 90% [1]. Frequent clinical and subclinical arousals as well as changes in the amount of time spent in a particular stage of sleep independent of nocturnal seizures or AED use have been described in patients with epilepsy [5]. Frequent phase shifts increase the frequency of seizures and interictal epileptiform discharges [6]. In turn, both nocturnal and daytime complex partial seizures fragment sleep due to frequent awakenings, an increase in the number of stage shifts, a reduction in the duration of REM and slow wave sleep, and prolonged sleep onset and REM latency [7–11]. In patients with temporal lobe complex partial seizures, nocturnal seizures reduce sleep efficiency, decrease stages 2 and 4 sleep, and increase stage 1 sleep [11].

Drowsiness or daytime somnolence seems a more prominent adverse effect of older AEDs with a greater incidence of somnolence in patients on combinations of antiepileptic agents [12]. Rapid escalation of daily dosing is an additional factor predisposing to a greater chance of reporting a decreased daytime vigilance. As a rule, tolerance develops shortly after initiation of therapy; however, in some patients the complaint of drowsiness might be persistent and, occasionally, may lead to poor compliance or discontinuation of the prescribed agent. The Multiple Sleep Latency Test (MSLT) and Maintenance Wakefulness Test (MWT) are the most widely used objective measures of degree of daytime somnolence [12–14] that allow quantification and refinement of subjective reports of sleep disturbances in patients with epilepsy [13]. The clinical role of other electrophysiological modalities such as quantitative EEG is still to be determined [15].

Insomnia is defined by DSM-IV as difficulty initiating or maintaining sleep, nonrestorative sleep, and significant impairment in daytime functioning for at least 1 month in duration. Research criteria defines insomnia as sleep latency of more than 30 minutes, sleep efficiency of less than 85%, and sleep disturbance occurring more than 3 times per week [16]. The prevalence of chronic or severe insomnia in the general population has been estimated to approach 10% [17]. Vendrame et al. utilized a questionnaire-based survey of 152 patients with the diagnosis of epilepsy. The prevalence of moderate and severe insomnia amongst this group was 51%, with a stronger association in patients on a higher number of AEDs and coexisting depressive symptoms. Both sleep quality and insomnia were significant predictors of lower quality of life. Insomnia did not correlate with worse seizure control. A potential limitation of the study was a lack of control for the presence of undiagnosed sleep apnea [18]. Other authors reported similar insomnia rates (50% and 52%) in adult patients with a diagnosis of epilepsy [3]. Reported rates of insomnia in epilepsy patients for specific AEDs are 2.2% (CBZ), 4.9% to 6.4% (LTG), 4.2% to 6.3% (LEV), 5% (PGB), 2.3% (TPM), 3.4% (VPA), and 6.6% (VGB) [19].

3. Effect of AEDs on Sleep Architecture

First-generation AEDs (barbiturates, benzodiazepines, phenytoin, and phenobarbital) tend to reduce the amount of time spent in REM and slow wave sleep. They also tend to fragment nighttime sleep by increasing the number of arousals and stage shifts while promoting daytime sleepiness [9, 20]. These agents tend to reduce the length of time spent in REM sleep, which is implicated in learning, memory processing, and brain plasticity. The proportion of REM sleep is increased in childhood and after intensive cognitive tasks; its prolongation and improved quality positively influence daytime cognitive performance. Sleep consolidation observed with the newer generation of AEDs may contribute to reduction of seizure threshold in susceptible patients [5]. The use of AEDs without detrimental effect on "essential sleep" may lead to increased quality of life measures [10]. Effects of particular AEDs on specific parameters of MSLT are summarized in Table 1.

3.1. Phenytoin (PHT). PHT inhibits voltage-gated use-dependent sodium channels. Subjective somnolence, sedation, or sleep disturbance have been reported in 23.1% of patients with epilepsy on PHT therapy [19]. PHT leads to a reduction in sleep efficiency, a decrease in sleep latency, and shortening of light sleep stages (N1 and N2) as well as the REM phase of the sleep cycle. Slow wave sleep increases in duration or does not change. Acute effects of PHT administration include a decrease in sleep-onset latency and the light stages of sleep with concomitant increase in slow wave sleep (SWS). The chronic use of PHT leads to an increase in the duration of light stages of sleep and a decrease in SWS [5, 6, 10, 21].

3.2. Phenobarbital (PBT). PBT binds to the $GABA_A$ receptor, enhancing the influx of chloride ions. It reduces the number of awakenings and sleep latency while increasing the length of NREM sleep and reducing REM phase duration [5, 6, 10].

3.3. Valproic Acid (VPA). VPA inhibits GABA degradation, blocks voltage-gated sodium channels, and reduces calcium currents. Subjective somnolence has been reported in 2.3% to 45% of patients with epilepsy on VPA therapy [19]. Early studies in patients on VPA therapy reported no effects on sleep architecture with stabilization of sleep cycles. Other studies suggested that VPA increases the number of arousals, prolongs the light stages of sleep and NREM phase, and decreases the length of the REM phase [5, 6, 10].

3.4. Carbamazepine (CBZ). The anticonvulsant effect of CBZ is mediated through inhibition of voltage-gated sodium channels. Subjective somnolence has been reported in 22% to 32.3% of patients with epilepsy on CBZ therapy [19]. Gigli et al. compared subjective and objective indices of daytime somnolence in patients with newly-diagnosed temporal lobe epilepsy with results from a group of healthy volunteers. Subjects from both groups were on 400 mg twice a day dosing of CBZ for a duration of one month. Polysomnography was performed to assess changes in sleep architecture. The initial administration of CBZ leads to an increase in the number of sleep stage shifts, a reduction in REM sleep, increased

Table 1: Influence of anticonvulsant medications on sleep cycle architecture.

	Sleep latency	Arousals	Stage 2/N2	Slow wave sleep	Rapid eye movement sleep	Sleep efficiency
BDZ	↓	↓	↑	↓	↓	↑
BRB	↓	↑	↑	↓	↓	–
PBT	↓	↓	↑	–	↓	↑ or ↓
PHT (acute)	↓	↑	↓	↑	–	
PHT (chronic)	↓	↓	↓	↑ or – or ↓	– or ↓	↓
CBZ (single dose)	↓		↓	↑ or –	↓	↑ or ↓
CBZ (chronic)	↓	↓	–	–	– or ↓	– or ↓
VPA	–	↑	↑	↑ or –	– or ↓	–
FBM						↓
LTG+	–	↓	↑	↓	↑	↑
LEV			↑	↑	↓	↑
ZNS+	–	–	–	–	–	–
TPM						
GBP	–	–	–	↑	–	–
GBP+	–	↓	↓	↑	↑	↑
PGB	↓	↓	↓	↑	–	↑
TGB	–		–	↑	–	↑
ETX		↑	↑	↓	↑	↓
VGB	–	–			– or ↓	
LCM						
OXC						
PPN						

BDZ: benzodiazepine, BRB: barbiturate, PBT: phenobarbital, PHT: phenytoin, CBZ: carbamazepine, VPA: valproate, FBM: felbamate, LTG: lamotrigine, LEV: levetiracetam, ZNS: zonisamide, TPM: topiramate, GBP: gabapentin, PGB: pregabalin, TGB: tiagabine, ETX: ethosuximide, VGB: vigabatrin, LCM: lacosamide, OXC: oxcarbazepine, and PPN: perampanel; +: add-on therapy; –: no changes; empty square: no data available.

fragmentation of REM sleep, and a significant reduction in sleep latency. Upon completion of the 1-month trial period the aforementioned effects on sleep architecture were reversed, with values not significantly different from baseline measures [5, 6, 10, 21, 22]. An increase in slow wave sleep duration and sleep efficiency were the significant finding when Cho et al. evaluated 15 patients with partial epilepsy on 400 mg/day of CBZ-CR [23].

3.5. Ethosuximide (ETX). ETX selectively inhibits T-type calcium channels in thalamic neurons. It has been reported to increase REM sleep phase, reduce SWS, enhance the light stages of sleep, and increase the number of awakenings after sleep onset (cited in [6, 10]).

3.6. Benzodiazepines (BDZ). The antiepileptic mechanism of action of BDZs is associated with binding to $GABA_A$ chloride channels, which contribute to increased neuronal inhibition. Subjective somnolence has been reported in 25% to 33.3% of patients with epilepsy on diazepam therapy [19]. The use of benzodiazepines has classically been associated with enhanced sleep-onset latency, increased length of the light stages of sleep, decreased SWS, prolonged REM sleep latency, and reduced overall REM sleep duration. The number of arousals after falling asleep is significantly decreased in patients on chronic BDZ therapy (cited in [6, 10]).

3.7. Lamotrigine (LTG). Inhibition of presynaptic voltage-sensitive sodium channels and impairment of glutamate release are likely the main antiepileptic mechanisms of lamotrigine [24]. Drowsiness is one of the most common side effects and is dose dependent. Hirsch et al. equated drowsiness with psychomotor slowing, fatigue, or lethargy. The authors observed drowsiness requiring a dose change in 5.7% of patients ($n = 811$; $P < 0.0001$). The same group observed nondose-dependent insomnia in 1.1% ($P < 0.6449$) of patients that lead to dose adjustment [25]. A higher insomnia rate of 6.4% was reported by Sadler [26]. Foldvary et al. investigated an effect of add-on LTG on sleep perception, sleep architecture, and daytime alertness in 10 patients taking either phenytoin (PHT) or carbamazepine (CBZ). Polysomnography demonstrated a statistically significant increase in N2 sleep stage and reduction in N3 sleep stage. A nonstatistically significant increase in REM duration was reported [5]. The majority of subjects experienced decreased sleep latency and improved consolidation of nocturnal sleep. One patient reported more frequent daytime napping. Varying data were reported by Placidi et al. who performed polysomnography

in 13 pharmacologically-resistant patients treated with LTG. There were a significant prolongation of REM sleep and a nonsignificant decrease in N3 sleep stage duration in these patients [24].

3.8. Zonisamide (ZNS). The antiepileptic effects of zonisamide are mediated through antagonism of voltage-dependent T-type calcium channels, inhibition of voltage-sensitive sodium channels, glutamate blockade, induction of γ-aminobutyric acid (GABA) release, and inhibition of carbonic anhydrase. Brodie et al. randomized 351 patients to receive an adjunct seizure treatment of zonisamide at escalating doses or a placebo treatment. Somnolence was reported in 5.4% of patients within the 100 mg/day dosing group, 3.6% of patients within the 300 mg/day group, and 14.4% of patients within the 500 mg/day group [27]. Romigi et al. evaluated the effects of ZNS on nocturnal sleep and daytime vigilance in 12 patients with localization-related epilepsy. Patients were evaluated with PSG, MSLT, the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Scale (ESS) prior to and following 3 months of ZNS treatment. There was no statistical significance detected for any of the assessed measures upon completion of the monitoring period [4].

3.9. Levetiracetam (LEV). The mechanism of action responsible for the antiepileptic effects of levetiracetam is likely modulated by binding to synaptic vesicle protein 2A (SV2A), a transmembrane protein involved in calcium-dependent presynaptic neurotransmitter release [28]. In clinical trials somnolence has been reported in 9.4% of patients taking 1,000 mg/d as an add-on therapy (difference from placebo was 5%) [29], in 11.3% of patients taking 2,000 mg/d as an add-on therapy (difference from placebo was 7%) [29] and in 6.1% of patients taking 3,000 mg/d as an add-on therapy ($P < 0.584$; difference from placebo was 2.3%) [30]. Another trial reported 20.4% of patients complaining of daytime sleepiness while taking 1,000 mg/d as an add-on therapy (difference from placebo was 6.7%) as compared to 18.8% of patients taking 3,000 mg/d as an add-on therapy (difference from placebo was 5.1%) [31]. Tsai et al. evaluated efficacy and safety of levetiracetam therapy in 47 Taiwanese patients. Somnolence was the most commonly reported adverse event: 40.4% in the experimental group and 14.9% in the placebo group. The degree of somnolence was mild in >80% of reported instances. The authors attributed the overall higher incidence of somnolence in the study to the greater degree of concomitant antiepileptic therapy that was reported in the United States and European studies [32]. Cicolin et al. obtained polysomnography and Multiple Sleep Latency Tests in 14 healthy adults treated with ≤2,000 mg/day of levetiracetam. There was a significant increase in time spent in all NREM stages with a relative decrease in time spent in REM sleep. Overall, LEV demonstrated a propensity for sleep consolidation without detrimental effect on daytime vigilance [33]. Bell et al. followed 16 patients with a history of partial epilepsy on stable carbamazepine monotherapy and 12 volunteers after administration of a single dose of 1000 mg of levetiracetam or placebo. The significant findings were an increase in total time spent in stages 2 and 4 (in patients only) of sleep and prolongation of REM latency (in volunteers only). Patient subjects reported having more restful sleep while volunteers were less alert and groggier on waking [34]. A questionnaire-based survey of 288 patients on chronic LEV therapy (90% on polytherapy) revealed an association between sleep problems and the presence of negative behavioral change. In contrast, positive behavioral changes were associated with increased arousal and better subjective cognitive performance [35]. An increase in sleep efficiency was the only significant finding when Cho et al. evaluated 16 patients with partial epilepsy on 1000 mg/day of LEV [23].

3.10. Topiramate (TPM). Topiramate promotes GABA-facilitated inhibition, blocks voltage-dependent sodium channels, modulates voltage-dependent calcium channels, and acts as an antagonist of AMPA receptors [6, 10]. Add-on trials reported a higher frequency of somnolence in patients receiving TPM [36] as compared to gradual titration monotherapy trials [37]. Reife et al. analyzed pooled data from six double-blind, placebo-controlled trials where TPM was used as an adjunctive therapy in 743 adult patients with a diagnosis of localization-related epilepsy. Somnolence was reported in 30% of patients taking 200–400 mg/day and in 28% of patients taking 600–1,000 mg/day. Nearly 90% of central nervous system adverse events were rated as mild or moderate, with the majority occurring shortly after TPM therapy initiation and resolving with continued treatment. Daytime sleepiness was cited as the most common reason for cessation of a TPM regimen, amounting to 3.2% of all discontinuations. Rapid titration was one of the predisposing factors for development of adverse side effects [38]. Glauser summarized data from six clinical trials of topiramate: somnolence was reported by 26.7%, 26.5%, 16.9%, 19.7%, and 27.7% of patients at respective doses of 200, 400, 600, 800, and 1000 mg/day. In trials with adjunctive use of TPM, somnolence was reported in 29% of subjects, whereas, with monotherapy, somnolence was reported in only 13% of patients [36]. When TPM 50 mg/day or 500 mg/day was used as monotherapy in patients with a diagnosis of localization-related epilepsy, somnolence was reported in 14% [39]. An Italian study by Bonanni et al. followed 14 newly diagnosed, pharmacotherapeutically naïve patients with localization-related epilepsy after initiation and titration of up to a 200 mg daily dose of TPM monotherapy for a 15-week period. The amount of daytime sleepiness was measured with the Epworth Sleepiness Scale and the Multiple Sleep Latency Test. Psychomotor performance was evaluated by simple and choice visual reaction times. Patients within the treatment group demonstrated no statistical variation in a daytime vigilance profile or psychomotor performance when compared to similar measures in control subjects [40].

3.11. Gabapentin (GBP). Gabapentin is an amino acid that was originally synthesized as a structural analogue of GABA, an inhibitory neurotransmitter in the adult brain. Even though GBP might increase the rate of GABA synthesis in rat brains, the antiepileptic qualities of this AED in humans are likely secondary to glutamate synthesis modulation and

inhibition of voltage-sensitive calcium channels [10]. Subjective somnolence has been recorded in 12.1% of patients with epilepsy on GBP therapy [19]. Foldvary-Schaefer et al. investigated the effects of 1,800 mg/day of GBP on sleep architecture and daytime vigilance in ten healthy adult volunteers. The only significant finding reported by the authors was an increase in baseline SWS in the treatment group. When compared to the control group, results were not statistically significant [9]. Placidi et al. evaluated ten patients diagnosed with partial epilepsy after 3 months of stable treatment with 1,800 mg/day of GBP. Polysomnography demonstrated significantly increased REM sleep percentage, prolonged REM mean duration, a decreased number of awakenings, and reduced duration of the N1 stage of sleep [6]. An independent study by Placidi et al. evaluated 18 patients with refractory partial seizures undergoing 4 months of stable treatment with 1800 to 2400 mg/day of GBP. There was a significant increase in REM and SWS percentage, a reduction in the number of awakenings, and a decrease in the length of stage 1 sleep. Sixteen patients reported improvement in sleep quality. There were no significant changes in frequency of interictal epileptiform discharges as evidenced by EEG recording [41].

3.12. Pregabalin (PGB). Pregabalin binds to central nervous system voltage-gated calcium channels demonstrating analgesic, antiepileptic, and anxiolytic effects. Somnolence was reported in 30.1% (versus 12.2% in placebo group) of patients taking 600 mg/day divided into two doses, in 23.4% (versus 12.2% in placebo group) of patients taking 600 mg/day divided into three doses [42], and in 6.1% to 17.4% of patients taking 150 mg/day [43, 44]. This adverse effect seems to be mild or moderate in intensity, occurring within the first two weeks of therapy initiation [45]. When given to 24 healthy volunteers, pregabalin increased time spent in SWS, decreased the number of awakenings, increased total sleep time, reduced sleep-onset latency, and improved sleep efficiency [46]. A randomized, placebo-controlled study of 17 patients with well-controlled partial seizures utilizing polysomnography and subjective sleep questionnaires to explore the effects of 300 mg/day of PGB was performed by de Haas et al. The results demonstrated subjective improvement in the number of awakenings but failed to reveal a statistical significance when analyzed with polysomnography [47]. Romigi et al. compared results of polysomnography and the Epworth Sleepiness Scale in 12 patients with a history of medically refractory seizures before and after a 3-month add-on treatment period with PGB. The authors reported a significant increase in the REM phase and decrease in stage 2 sleep percentage [48].

3.13. Vigabatrin (VGB). VGB increases GABA concentration by inhibiting GABA transaminase facilitated GABA uptake [49]. Subjective somnolence has been reported in 11.3% to 25.7% of patients with epilepsy on VGB therapy [19]. Initial reports indicated no changes in polysomnographic and daytime somnolence measures with add-on VGB therapy [10]. Siegel et al. showed prolongation of REM sleep latency with vigabatrin use in three epilepsy patients [50].

3.14. Perampanel (PPN). The proposed antiepileptic effects of perampanel are exerted via noncompetitive antagonism of the AMPA- (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-) type glutamate receptor [51]. Subjective somnolence varies depending on the administered dose regimen; it has been reported in 12.2% of patients on 2 mg/day, 5.9% to 20% in patients on 4 mg/day, 12.4% to 26.7% in patients on 8 mg/day, and 17.2% to 19.7% in patients on 12 mg/day [52–57].

3.15. Felbamate (FBM). FBM acts on voltage-sensitive calcium channels, NMDA receptors, and, to a milder degree, voltage-sensitive sodium channels [49]. Grosso et al. evaluated 53 children under the age of 4 years on FBM therapy. Somnolence was reported in 13% of patients; an additional 9% of patients had unspecified sleep disturbance complaints [58]. In some epileptic patients felbamate precipitated insomnia with acute and chronic therapy [10].

3.16. Tiagabine (TGB). TGB inhibits GABA reuptake, leading to increased concentrations of the neurotransmitter [49]. Subjective somnolence has been reported in 1.1% of epilepsy patients on TGB therapy [19]. TGB has been reported to increase the duration of SWS [19].

3.17. Lacosamide (LCM). LCM exhibits its antiepileptic properties through selective slow inactivation of voltage-gated sodium channels [59]. Subjective somnolence has been reported in 5.1% (for the IV formulation) to 9.7% of patients with epilepsy on LCS therapy [19].

3.18. Oxcarbazepine (OXC). The primary antiepileptic mechanisms of OXC are via voltage-sensitive sodium and calcium channel inhibition [49]. Subjective somnolence has been reported in 15.7% of patients with epilepsy on OXC therapy [19].

4. Chronoepileptology

The emerging field of chronoepileptology aims to explore the relationship between seizures and circadian rhythms, with an ultimate goal of utilizing AEDs or neurostimulation in targeted, specific patient populations or individual patients suffering from epileptic seizures in order to maximize their therapeutic effects and minimize adverse events [60]. Circadian rhythms constrained by a 24-hour cycle, under the influence of ambient time clues such as daylight and darkness at night, are an ubiquitous feature of most organisms. The pacemaker underlying the cyclical nature of physiologic, metabolic, and behavior changes is located in the anterior hypothalamic suprachiasmatic nuclei (SCN) in mammals [61, 62]. The circadian system determines the onset of the sleep cycle as well as the shifting between and duration of different sleep stages. Projections from the SCN affect the thalamic and limbic systems—to name a few—networks implicated in epileptogenesis and propagation of epileptic discharges.

A fluctuation of neurotransmitter and hormone concentrations throughout the sleep-awake cycle has been shown

to correlate with a propensity towards epileptic activity. An increasing concentration of adenosine during wakefulness exhibits anticonvulsant properties [61]. Serotonin receptor agonists increase seizure threshold [63]. A nocturnal melatonin peak produced by the pineal body under direct influence of the SCN may have both anti- and proconvulsant effects depending on the administered dose [64–66]. A rising cortisol concentration before awakening is presumed to be protective against seizures [61].

A predilection of a particular type of seizure for a specific portion of the sleep cycle has been described. Seizures that are features of idiopathic generalized epilepsies are more likely to occur during drowsiness, slow wave sleep, and awakening from slow wave sleep in animal models [67]. A study of patients with temporal and frontal lobe seizures by Hofstra et al. used salivary levels of melatonin to determine the timing of seizures in relation to circadian rhythms. The peak frequency of temporal lobe seizures occurred within the 6 hours prior to the daily melatonin concentration elevation whereas frontal lobe seizures were most frequent in the 6 to 12 hours after the melatonin concentration increase [62].

Intentional changes in administration schedule of AEDs to accommodate circadian rhythms have been reported in patients with epilepsy. Hofstra et al. evaluated 208 patients with an established diagnosis of epilepsy utilizing the Morningness-Eveningness Questionnaire (MEQ). Patients were subdivided into morning, evening, and intermediate circadian types. All three groups demonstrated adaptation of antiepileptic therapy administration to their circadian rhythm with significant delay of administration on workdays compared to free days [68]. This finding illustrates both the tendency to adjust to the work schedule by the patients and increasing probability of breakthrough seizures on off-work days in the light of significant delay of AED administration. A tailored increase of pharmacological therapy in pediatric patients with nocturnal and early-morning seizure leads to higher rates of seizure freedom or spell frequency reduction in a study by Guilhoto et al. [69]. The presence of increased CNS responsiveness to pharmacologic agents during particular phases of the sleep-awake cycle has been proposed as a mechanism responsible for improved seizure control.

5. Conclusion

The influence of seizures on sleep has been well established [12, 70–73]. Although AEDs are only partly responsible for sleep cycle disturbance, an understanding of their impact can help clinicians tailor regimens that prevent unnecessary worsening of sleep quality. Other factors play significant roles in the reciprocal relationship between epilepsy and sleep. The risk factors predisposing to worsening sleep disturbances in adults with epilepsy include the use of older generation AEDs, nocturnal seizures, poor seizure control, comorbid affective disorder, and underlying sleep disorder. In children, factors contributing to a higher likelihood of sleep disturbances are younger age, developmental delay, increased frequency of seizures, a diagnosis of symptomatic epilepsy, polypharmacy, and coexisting sleep disorder. Other important factors that influence the sleep cycle are the rate of AED dose escalation and duration of AED therapy. Newer generation AEDs generally tend to cause less disturbance of the sleep cycle and greater stabilization of sleep architecture. In addition, prolongation of REM sleep and improved sleep efficiency are potential benefits of some newer AEDs that may secondarily contribute to suppression of seizures and decreased epileptogenicity. The influence of circadian rhythms on epileptogenicity is a concept that has been revisited in recent years. A more profound understanding of the relationship between biological rhythmicity throughout the 24-hour awake-sleep cycle and the propensity to have epileptic seizures at particular times within the cycle will allow more directed application of timed AED therapy, personalized VNS parameter settings, changes in sleep hygiene, and/or hormone therapy.

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Review Article

Why Are Seizures Rare in Rapid Eye Movement Sleep? Review of the Frequency of Seizures in Different Sleep Stages

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Since the formal characterization of sleep stages, there have been reports that seizures may preferentially occur in certain phases of sleep. Through ascending cholinergic connections from the brainstem, rapid eye movement (REM) sleep is physiologically characterized by low voltage fast activity on the electroencephalogram, REMs, and muscle atonia. Multiple independent studies confirm that, in REM sleep, there is a strikingly low proportion of seizures (~1% or less). We review a total of 42 distinct conventional and intracranial studies in the literature which comprised a net of 1458 patients. Indexed to duration, we found that REM sleep was the most protective stage of sleep against focal seizures, generalized seizures, focal interictal discharges, and two particular epilepsy syndromes. REM sleep had an additional protective effect compared to wakefulness with an average 7.83 times fewer focal seizures, 3.25 times fewer generalized seizures, and 1.11 times fewer focal interictal discharges. In further studies REM sleep has also demonstrated utility in localizing epileptogenic foci with potential translation into postsurgical seizure freedom. Based on emerging connectivity data in sleep, we hypothesize that the influence of REM sleep on seizures is due to a desynchronized EEG pattern which reflects important connectivity differences unique to this sleep stage.

1. Introduction

A bidirectional relationship between epilepsy and sleep has been observed since the time of Hippocrates [1]. It was not until the first formal characterization of sleep stages that this relationship became successively attuned to each specific sleep stage. It became apparent that seizures may preferentially occur during certain phases of sleep with the least likelihood of occurrence in rapid eye movement (REM) sleep. The purpose of this review is to focus on the impact of REM sleep on seizures. We discuss REM sleep physiology, a review of the available literature regarding seizures during REM sleep, and a consideration of the potential mechanisms which may underlie this intriguing but often overlooked phenomenon.

2. REM Sleep Physiology

Based on a wealth of animal and human data accumulated since the discovery of REM sleep in 1953 [2], an exciting and coherent model of REM sleep physiology has emerged. In the pontomesencephalic junction of the brainstem, there are two populations of cholinergic neurons in the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) [3]. Within these populations, there is a subset of cells that are most active in REM sleep, as well as another subset, which is active in both REM sleep and wakefulness [4–7].

Of the neurons whose spontaneous firing rate is highest in REM sleep, some exhibit a spontaneous bursting depolarization pattern due to a "low threshold spike" inward calcium current [8]. Through muscarinic greater than nicotinic

acetylcholine receptors [9], connections from the LDT and PPT excite populations of neurons in the pontine reticular formation (PRF) and mesencephalic reticular formation (MRF) which serve as "effector cells" responsible for the following dissociable characteristics of REM sleep:

(1) low voltage fast electroencephalographic (EEG) activity,

(2) rapid eye movements (REMs),

(3) muscle atonia.

Low voltage fast activity on the EEG is due largely to depolarization of the thalamus by cholinergic MRF neurons [8]. Thalamic activation allows transmission of information to the cortex and subsequent EEG desynchronization which contrasts with the generally synchronized high-voltage activity of slow-wave sleep [10]. There is also evidence that another cholinergic subpopulation ventral to the dorsolateral PRF depolarizes the thalamus; however, the resultant EEG resembles more the waking state than REM sleep [11]. Furthermore, the LDT and PPT may directly activate cholinergic centers in the basal forebrain which has further excitatory connections to hippocampus and cortex [12–15]. In addition, there may be an element of cortical disinhibition as the basal forebrain also contains gamma-aminobutyric acid (GABA) ergic neurons which may be stimulated to deactivate inhibitory interneurons with further projections to hippocampus and cortex [16, 17].

Rapid eye movements are heralded by discharges, known as pontogeniculooccipital (PGO) waves, from a dorsorostral subpopulation of cholinergic PRF neurons which project to the occipital lobe via the lateral geniculate nucleus (LGN). The presence of PGO waves precedes REMs by 3–5 waves and low voltage fast activity by 30–60 seconds [18].

Muscle atonia is partly the result of neurons in the dorsolateral PRF [8]. Through glutamatergic and/or GABAergic connections [19], these neurons project to the bulbar reticular formation (BRF) which inhibits lower motor neurons via GABA and glycine [20]. Muscle atonia is also the result of loss of serotonergic and noradrenergic tone as these neurotransmitter systems are silent in REM sleep [21–24].

Collectively the LDT, PPT, PRF, and MRF are known as the "REM-on" neurons. In contrast, there are populations of "REM-off" neurons mainly in the serotonergic midline raphe nuclei and noradrenergic locus coeruleus (LC) [25–28]. Of the raphe nuclei, the chief nucleus is the dorsal raphe (DRN) [29] but others (such as the linearis centralis [30], centralis superior [31], raphe magnus [32, 33], and raphe pallidus [34]) have been implicated. Furthermore, there are also aminergic populations in the anterior pontine tegmentum near the pontomesencephalic junction as well as other "stray" neurons throughout the brainstem with REM-off characteristics [8]. While firing rates of REM-on neurons are the highest in REM sleep, firing of the REM-off neurons is maximal in wakefulness [35].

The REM-on and REM-off neurons mutually antagonize each other. The model first proposed by McCarley and Hobson in 1975 [36] was characterized as a reciprocal interaction model based on Lotka-Volterra equations originally used to describe interactions between prey (i.e., REM-on) and predator (i.e., REM-off) populations. In this model, REM-on neurons initially grow exponentially by positively feeding back onto each other. At the same time, they activate REM-off neurons as a form of negative feedback. After being activated, REM-off neurons inhibit REM-on neurons and simultaneously exert negative feedback pressure on themselves.

With respect to anatomical and functional correlation of REM-on neurons in the model, there exists a positive feedback connection between LDT/PPT and PRF/MRF neurons [3]. Furthermore, a negative feedback connection has been found between LDT/PPT and LC neurons [37]. Regarding REM-off neurons, serotonin and noradrenaline (presumably from the DRN and LC, resp.) have been found to inhibit bursting LDT neurons [38]. There also exist negative feedback inhibitory recurrent collateral pathways for both the DRN and LC [8].

The reciprocal interaction model provides one method of explaining the 90-minute alternations between 30-minute REM sleep periods and NREM sleep periods over the course of a usual night. In order to account for the first shorter REM episode, which typically occurs 70–120 (on average 90) minutes after sleep onset, subsequent versions of the model have included a "limit cycle" modification [39].

Furthermore, the hormone orexin (also known as hypocretin), which is secreted by neurons in the lateral hypothalamus, additionally fine-tunes transitions into and out of REM sleep by diurnally gating REM sleep over the course of the entire sleep-wake cycle [53]. One potential mechanism is through strategic and selective excitation of REM-off neurons [8, 54–57]. Also manufactured in the lateral hypothalamus by neurons intermixed with orexin neurons [58–60], melanin-concentrating hormone is another recently discovered agent which may play a similar diurnal role through an inhibitory, rather than excitatory, mechanism [58, 61, 62].

3. Clinical Observations of Seizures in REM Sleep

Initial studies on the frequency of interictal and ictal events during REM sleep were largely anecdotal and consisted primarily of case reports. Studies were heterogeneous in terms of seizure/epilepsy classification (e.g., waking epilepsy, definitely symptomatic epilepsy), patient population (e.g., severity of epilepsy, use of antiepileptic drugs), use of the EEG (e.g., 10–20 system, montages, method of detecting abnormalities, inclusion of benign variants as abnormal features), use of the polysomnogram (PSG) (e.g., use of electromyography, definition of wakefulness and sleep stages), and outcome measures of both interictal and ictal events. Gradually, however, the methodology for recording and scoring became more standardized and this permitted comparison.

In this review, the total number of events in wakefulness and each sleep stage was extracted for each study examined. Rates of interictal and ictal events in wakefulness and each sleep stage were also extracted. If rates were not explicitly provided, then they were calculated by dividing the number

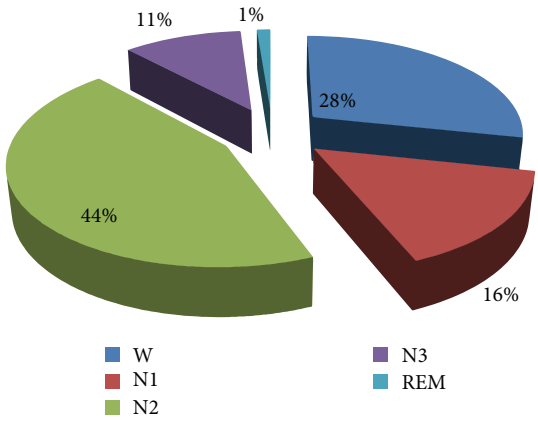

Figure 1: Raw sum of focal seizures.

of events by the duration of wakefulness and/or each sleep stage when available. To facilitate comparison, each rate was then divided by the rate for REM sleep in order to determine an "indexed" rate. In averaging these indexed rates, each study was not treated equally. Rather, a "weighted mean" was produced by weighting each study based on the number of patients contained with each.

If individual sleep stages were not separated, then the same rate was used for each constituent stage (e.g., a combined N1/N2 rate was used individually as a rate for N1 and a rate for N2). With respect to numbers of events, this was divided equally among the constituent stages (e.g., a total of 33 seizures for N1/N2/N3 were counted as 11 for each stage). Formerly stage III and stage IV sleep were combined into stage N3 for analysis. Depending on the study, the definition of wakefulness may have included wake periods after sleep onset (WASO), nocturnal awakenings, morning awakenings, and/or samples of fully alert daytime wakefulness. As studies were divergent, statistical significance could not be calculated.

3.1. Focal Seizures. A total of 542 patients with a collective 1990 seizures over 9 studies [40–43, 75–79] from 1987 to 2006 were included. Two studies [78, 79] were conducted using intracranial depth electrodes on patients classified with temporal or extratemporal epilepsy. The distribution of the 1990 seizures in wakefulness and specific sleep stages is shown in Figure 1.

The percentage of focal seizures during REM sleep over total recording time was extremely low (1%) over all these studies. However, because these studies did not provide specific durations, the length of recording may have led to artificial overinflation or underinflation of data. To address this issue, Table 1 provides a rate of focal seizure activity from four of these studies [40–43] where duration was provided.

Relative to REM sleep, the focal seizure rate was 7.83 times higher in wakefulness, 87 times higher in stage N1 sleep, 68 times higher in stage N2 sleep, and 51 times higher in stage N3 sleep. These data imply that focal seizures were most frequent in NREM sleep, intermediate in wakefulness, and lowest in REM sleep. However, the increased rate in wakefulness was highly variable with the weighted mean being powered by a single study [41]. In comparison, the study with the largest number of patients conducted by Herman et al. [43] yielded no seizures in either REM sleep or wakefulness.

Table 1: Relative focal seizure rates*.

Paper/sleep stage	W	N1	N2	N3	REM
Minecan et al. 2002 [40]	0.00	6.00	7.00	5.00	1.00
Crespel et al. 1998 [41]—FLE	133.42	14.59	14.59	14.59	1.00
Crespel et al. 1998 [41]—TLE	55.08	1.67	1.67	1.67	1.00
Terzano et al. 1991 [42]	0.00	5.52	2.16	3.77	1.00
Weighted mean	7.83	87.25	67.84	50.78	1.00

*Herman et al. 2001 [43] was included in weighted mean but could not be displayed as a relative rate because no seizures occurred in REM sleep.

Table 2: Relative generalized discharge rates.

Paper/sleep stage	W	N1	N2	N3	REM
Halász et al. 2002 [44]	8.14	14.53	10.47	3.49	1.00
Parrino et al. 2001 [45]		3.50	3.50	3.50	1.00
Horita et al. 1991 [46]	1.43	3.54	0.75	0.00	1.00
Autret et al. 1987 [47] /1997 [48]	1.37	1.50	1.50	2.25	1.00
Autret et al. 1987 [47] /1997 [48]—Pediatrics	2.30	3.66	3.66	4.91	1.00
Touchon 1982 [49]	5.05	3.26	0.10		1.00
Kellaway et al. 1980 [50]	1.68	5.63	5.63	5.63	1.00
Sato et al. 1973 [51]		3.32	16.04	43.45	1.00
Ross et al. 1966 [52]	4.94	3.12	3.94	11.06	1.00
Weighted mean	3.25	3.10	3.13	6.59	1.00

3.2. Primary Generalized Seizures. A total of 256 patients with idiopathic generalized epilepsy were included among 7–9 studies [44–52] who ranged in age from 4 to 46. Specific subsets of idiopathic generalized epilepsy included juvenile myoclonic epilepsy, childhood absence epilepsy, and more generally "petit mal" and "grand mal" seizures in older studies.

Table 2 demonstrates that, relative to REM sleep, the generalized discharge rate was 3.25 times higher in wakefulness, 3.1 times higher in stage N1 sleep, 3.13 times higher in stage N2 sleep, and 6.59 times higher in stage N3 sleep. In contrast to focal epilepsy, where data was available as shown in Table 3, no patients demonstrated maximal generalized discharges in REM sleep.

3.3. Specific Epilepsy Syndromes. Benign epilepsy of childhood with rolandic spikes (BECRS) is the best studied focal syndrome in terms of discharge frequency in REM sleep. A total of 110 patients aged 3–16 were examined by

Table 3: % patients with maximal generalized discharges per state.

Paper/sleep stage	W (%)	N1 (%)	N2 (%)	N3 (%)	REM (%)
Horita et al. 1991 [46]	0.0	100.0	0.0	0.0	0.0
Sato et al. 1973 [51]		0.0	8.3	91.7	0.0
Ross et al. 1966 [52]	23.1	7.7	7.7	61.5	0.0
Weighted mean	22.8	14.8	5.9	56.4	0.0

Table 4: Relative rolandic discharge rates.

Paper/sleep stage	W	N1	N2	N3	REM
Billiard et al. 1990 [63]	0.54	1.19	1.19	1.19	1.00
Dalla Bernardina et al. 1982 [64]	0.22	0.97	1.08	1.28	1.00
Weighted mean	0.27	1.00	1.10	1.27	1.00

Billiard et al. [63] and Dalla Bernardina et al. [64] in 2 separate studies.

Table 4 demonstrates that, relative to REM sleep, discharges were about 4 times lower in wakefulness, about the same in stage N1 sleep, 1.1 times higher in stage N2 sleep, and 1.27 times higher in stage N3 sleep. In another study by Dalla Bernardina et al. in 1975 [80], comment was made that children with rolandic spikes but without seizures have a marked deactivation of discharges in REM sleep while those with seizures do not.

In addition to focal syndromes, a few case reports have also explored the impact of REM sleep on the epileptic encephalopathies. In 1981, Billiard et al. [70] presented 2 patients with Landau-Kleffner Syndrome aged 3 and 6 years who had higher interictal discharge rates in stage N1/2 (113% of REM) and N3 (127% of REM) sleep. However, Genton et al. [81] later published a case report of a 3.5-year-old girl with lateralized activation of right temporal spike-wave complexes in REM sleep.

In 1982, Tassinari [82] described 19 cases of electrical status epilepticus in slow wave sleep (ESES). He noted that, in REM sleep, all electrical status disappeared with only 3 instances of electrographic seizures resuming at the end of the REM sleep period. Similarly in 1981, Hrachovy et al. [83] described 32 patients aged 1–43 months with infantile spasms. He also noted that all patients demonstrated less or no hypsarrhythmia on the EEG during REM sleep.

3.4. Focal Interictal Discharges. A total of 214 patients were included among 7–10 different studies [47, 48, 65–73] who ranged in age from 2 to 61 years. Three studies [71–73] were conducted using intracranial depth electrodes on patients classified with temporal, frontal, occipital, parietal, or limbic seizures.

Table 5 demonstrates that, relative to REM sleep, the focal interictal discharge rate was 1.11 times higher in wakefulness, 1.75 times higher in stage N1 sleep, 1.69 times higher in stage N2 sleep, and 2.46 times higher in stage N3 sleep. These data imply that discharge rates are highest in NREM sleep (particularly stage N3) and comparable between wakefulness and REM sleep with the latter having a slightly lower firing rate.

Table 5: Relative focal interictal discharge rates.

Paper/sleep stage	W	N1	N2	N3	REM
Clemens et al. 2005 [65]	1.52	2.50	1.85	2.67	1.00
Clemens et al. 2003 [66]	0.41	1.56	1.48	2.46	1.00
Ferillo et al. 2000 [67]		0.91	1.09	1.81	1.00
Malow et al. 1998 [68]		2.45	3.79	7.39	1.00
Malow et al. 1997 [69]		2.38	4.50	7.13	1.00
Billiard et al. 1981 [70]—Symptomatic	0.84	1.68	1.68	1.68	1.00
Billiard et al. 1981 [70]—Definite	0.70	1.43	1.43	1.43	1.00
Autret et al. 1987 [47]/1997 [48]	0.44	1.18	1.18	1.15	1.00
Rossi et al. 1984 [71, 72]*	1.17	1.33	1.33	1.18	1.00
Montplaisir et al. 1982 [73]*	1.21		2.43		1.00
Weighted mean	1.11	1.75	1.69	2.46	1.00

*Intracranial depth electrode study.

Table 6: % patients with maximal focal discharges per state.

Paper/sleep stage	W (%)	N1 (%)	N2 (%)	N3 (%)	REM (%)
Clemens et al. 2005 [65]	11.1	11.1	0.0	66.7	11.1
Ferrillo et al. 2000 [67]		19.4	11.1	61.1	8.3
Sammaritano et al. 1991 [74]	2.5	3.8	3.8	77.5	12.5
Weighted mean	5.9	8.7	5.1	69.5	10.9

Although REM sleep had the lowest rate of focal interictal discharges overall, this did not mean that each individual patient necessarily had lower rates of discharges in REM sleep. As Table 6 shows, where data was available, a weighted mean 10.9% of patients had maximal interictal discharge rates in REM sleep. This was second only to stage N3 sleep. In the context of the findings in Table 1, this implies that while these patients had maximal discharge rates in REM sleep compared to wakefulness or other sleep stages, the absolute rate remained low.

In intracranial depth recordings, Rossi et al. [71, 72] showed that, in REM sleep, there was a selective increase in the rate of interictal discharges over the epileptogenic zone (defined as the region which after resection resulted in seizure freedom) when compared to other sampled parts

of the brain. While Wieser [84] commented on previous similar findings of increased REM sleep interictal discharge rates over the amygdala and supplementary motor area, he noted that these studies often considered benign variants as epileptiform [85, 86].

3.5. Selective Localization of Epilepsy in REM Sleep. Like seizure frequency in REM sleep, the impact of REM sleep on the distribution of interictal and ictal phenomena is controversial. The most powerful argument for clinically useful localization of an epileptogenic focus in REM sleep comes from a subset of tuberous sclerosis patients and a single temporal lobe epilepsy patient in studies by Ochi et al. [87] and Malow and Aldrich [88], respectively. In 6 of Ochi's patients, the semiology, neuroimaging, and other EEG were discordant in localizing the epileptogenic focus. Focal resection was undertaken in the hemisphere to which discharges were selectively lateralized in REM sleep. Four of six patients did well after surgery (Engel class I or II). In Malow's case report, 1 patient with bitemporal discharges selectively lateralized in REM sleep. After amygdalohippocampectomy in this hemisphere, the patient was rendered seizure-free for at least 3 years. For these patients, lateralization based on REM sleep alone was able to localize the epileptogenic zone in the midst of discordant data and predict seizure freedom.

Other studies have explored the localizing ability of REM sleep in relation to a "final" localization based on general concordance of all available data. 100% of unilateral temporal lobe patients with REM-lateralized interictal discharges or seizures were lateralized to the same hemisphere as the "final" localization. For NREM sleep, the concordance rate of interictal discharges and seizures was 100% and 94%, respectively. For wakefulness, it was a respective 88% and 94%. In patients where discharges were bitemporal, REM localization agreed with the final localization 100% of the time (compared to 81% in NREM and 100% in wakefulness). In an intracranial study by Lieb et al. [89], eight of 10 patients with REM-lateralized interictal discharges demonstrated statistically significant concordance with the final localization. Statistical significance for lower rates of concordance could not be established for wakefulness, "light sleep", or "deep sleep".

However, there remains controversy regarding the localizing value of interictal discharges. For example, in Lieb's study [89], two of 10 patients with REM-lateralized discharges were discordant with the final localization. Furthermore, Genton et al. [81] have described a case of Landau-Kleffner Syndrome in which spike rate dramatically increased and spread contralaterally during REM sleep. In an intracranial depth electrode study of 15 temporal lobe epilepsy patients, Montplaisir et al. [73] noted that spikes were often seen in areas outside the epileptogenic zone in the ipsilateral hemisphere as well as in homologous regions to the epileptogenic zone over the contralateral hemisphere.

4. How REM Sleep Could Affect Seizures

As previously discussed, the observed desynchronized EEG of REM sleep is the result of cholinergic MRF neurons depolarizing the thalamus which allows transmission of information to the cortex. Like REM sleep, the EEG of wakefulness is also desynchronized because cholinergic activity is likewise present.

In contrast, cholinergic neurons are less active in NREM sleep with the least activity occurring in deep slow-wave sleep (i.e., stage N3) [10]. Without afferent mesencephalic cholinergic stimulation, the thalamus is not depolarized. An inactive thalamus does not allow transmission of information to the cortex. Without the inhomogeneous stimulation afforded by afferently transmitted information through the thalamus, cortical neurons are then able to intrinsically fire in a synchronized fashion. This is reflected by the maximally synchronized EEG of stage N3 sleep.

To summarize, REM sleep and wakefulness represent states of maximal cortical synchrony, stages N1 and N2 sleep are states of intermediate synchrony, and stage N3 sleep represents a state of maximal cortical desynchrony.

4.1. Focal Interictal Discharges. When neurons exhibit asynchronous discharging behaviour at baseline, there is a reduced opportunity for spatial and temporal summation of any additional spontaneous depolarization [90, 91]. Such spontaneous depolarizations by populations of abnormally excitable neurons, in other words the "paroxysmal depolarizing shift", have been hypothesized to be the mechanism behind focal epilepsy and interictal epileptiform discharges [92].

The reduced opportunity for spatial and temporal summation of such abnormal depolarizations may account for the results contained within Table 5. These data demonstrate that the highest rate of focal interictal discharges is in stage N3 sleep. This is in contrast to the lowest discharge rate which occurs comparably across REM sleep and wakefulness.

Another possible mechanism by which cortical desynchrony may account for this disparity in focal discharge rates is through the emergence of regional antiepileptic "microrhythms". In contrast to the uniform global cortical synchrony of stage N3 sleep, there usually are distinct regional rhythms in more desynchronized states. For example, a posterior dominant alpha rhythm often exists in wakefulness. Even during the intermediately synchronized EEG of stage N2 sleep, there are regional sleep spindles located in the frontocentral regions bilaterally which, by definition, disappear with the onset of slow-wave sleep. Furthermore, a recent study has commented on "islands of hyperconnectivity" in REM sleep [93].

While the regional rhythms mentioned above are not known to be antiepileptic, another rhythm has been described, the hippocampal theta rhythm, which is also present in the desynchronized states of REM sleep and wakefulness [94]. In animal models, this rhythm has been shown to exert an antiepileptic effect [95].

However, the opposite may also be true and there could exist proepileptic regional rhythms in certain individuals. This may account for the interindividual variability in Table 6 which examined in which state of consciousness did a particular individual have the greatest rate of focal interictal

discharging. Despite comparable overall rates of focal interictal discharges in REM sleep and wakefulness among patients from all studies included for analysis, a respective 5.9% and 10.9% of individuals achieved maximal discharge firing rates in wakefulness and REM sleep.

4.2. Focal Seizures and Generalized Epilepsy. Similar to focal interictal discharges, focal seizures are also hypothesized to arise from the "paroxysmal depolarizing shift" [96]. However, subsequent organization is required to sufficiently activate and recruit surrounding neurons in order to transform a focal interictal epileptiform discharge into an ictal event [96]. Recruitment of surrounding neurons leads to loss of surround inhibition, and seizure activity then spreads contiguously via local "short" cortical-cortical connections [96]. Secondary generalization may occur if there is spread to more distant areas via "long" association pathways such as the corpus callosum [96].

Like secondarily generalized seizures, primary generalized epilepsy also involves spread via long pathways but through a mechanism distinct from the paroxysmal depolarizing shift. Both primary generalized ictal and interictal phenomena have been hypothesized to be the result of abnormally synchronized and reverberating thalamocortical networks [97]. The distinction between ictal from interictal events rests mainly on discharge duration (i.e., greater than 10 seconds) and presence of clinical correlate [98].

Tables 1 and 2 demonstrate that rates of focal seizures and generalized discharges occur most often in NREM sleep when compared to either REM sleep or wakefulness. The same mechanisms proposed to account for a relatively higher rate of focal interictal discharges in NREM sleep would also apply to focal seizures and primary generalized epilepsy.

Namely, the lower likelihood for spatial and temporal summation of aberrant spontaneous depolarizations in the cortically desynchronized states of REM sleep and wakefulness reduces the chance of spread along "short" pathways to surrounding neurons in focal epilepsy and "long" thalamocortical and association pathways in generalized epilepsy. Furthermore, should a desynchronized cortical milieu permit the emergence of regional antiepileptic microrhythms, this would present a further impediment to the spread of any aberrant depolarization.

However, unlike focal interictal discharges, the potential presence of proepileptic regional rhythms in certain individuals would not be expected to impact a primary generalized phenomenon. This is consistent with the results of Table 3 which demonstrate that among all patients in studies included for analysis, no individuals (0%) demonstrated a maximal discharge firing rate in REM sleep.

Returning to Tables 1 and 2, not only is it shown that rates of focal seizures and generalized discharges are lower in REM sleep and wakefulness, but rates are additionally lower in REM sleep compared to wakefulness. While both states of consciousness share a desynchronized EEG due to cholinergic activity, they differ greatly in terms of other neurotransmitter activity and in terms of connectivity.

Serotonergic neurons primarily located in the raphe nuclei, noradrenergic neurons in the locus coeruleus, and histaminergic neurons from the tuberomammillary nucleus demonstrate maximal firing rates in wakefulness and lowest firing rates during REM sleep [10]. These neurotransmitters are generally considered to produce arousal through widespread and usually excitatory effects on target neurons [10]. Such effects, present in wakefulness and absent in REM sleep, may account for recently discovered significant differences in connectivity between REM sleep and wakefulness.

An fMRI study [99] of the default network demonstrated substantially reduced connectivity in REM sleep when compared to wakefulness. The greatest difference appeared to be disconnection of the dorsomedial prefrontal cortex. This was validated by another study [100] examining functional connectivity by multichannel EEG which disclosed disconnection of anterior from posterior cortical areas in REM sleep. Loss of the organizing influence from the frontal lobes may be reflected by the often illogical and nonsensical content of dreams in REM sleep [101].

Because a loss of connectivity precludes the presence of synchrony, strategic losses of brain connectivity in REM sleep compared to wakefulness might explain any extra antiepileptic effect of REM sleep. As previously discussed, the greater the degree of desynchronization, the less likely the spatial and temporal summation of any aberrant spontaneous depolarization which would allow "spread" along "short" or "long" pathways in the brain.

4.3. Specific Epilepsy Syndromes. From the aforementioned case reports on the epileptic encephalopathies, REM sleep has been noted to usually have an antiepileptic effect. As an encephalopathy is, by definition, a spread-out and diffuse process, the reduced potential for such spread in the desynchronized environment of REM sleep may explain this observed antiepileptic effect.

In contrast, Table 4 demonstrates that the rate of rolandic interictal discharges in BECRS is higher in REM sleep than wakefulness. Like Table 2 which demonstrates a higher maximal rate of focal interictal discharges in REM sleep for certain individuals, the finding in Table 4 can also be explained by the presence of a proepileptic regional rhythm which may promote interictal discharging in the rolandic region.

4.4. Selective Localization. From the reviewed studies involving multifocal (i.e., tuberous sclerosis [87]) and focal [89] (i.e., temporal lobe [74, 88]) epilepsy, interictal discharges during REM sleep usually have a greater predictive value in selectively localizing an epileptogenic focus. Like the postulated mechanisms behind a lower rate of focal seizures and generalized discharges in REM sleep, selective localization may also be explained by the reduced chance of an aberrant spontaneous depolarization spreading—be it from a lower probability of spatial and temporal summation in a desynchronized cortical environment or the emergence of regional antiepileptic microrhythms.

However, there are also clearly described instances of false localization in the literature [73, 81, 89]. Like the postulated

mechanism behind a higher rate of interictal discharges in certain individuals and in certain syndromes such as BECRS, the presence of a proepileptic regional rhythm may skew the propagation patterns of focal interictal discharges so as to point to a false localization of the epileptogenic focus.

5. Conclusion

Sixty years after the discovery of REM sleep, a wealth of literature has commented on the effect of REM sleep on seizures. In our review, we have demonstrated that, compared to NREM sleep, REM sleep has a strong antiepileptic effect against focal interictal discharges, focal seizures, and generalized seizures. We also found that REM sleep has an additional antiepileptic effect compared to wakefulness against focal and generalized seizures.

While cases of false localization have been described, REM sleep has been demonstrated to have promise in helping localize epileptogenic foci with possible translation into post-surgical seizure freedom. The potential selective localizing value of REM sleep may argue for the use of dedicated sleep recordings in the presurgical evaluation of epilepsy.

Finally, we hypothesize that the impact of REM sleep on epilepsy is due to a maximally desynchronized EEG pattern which reduces the likelihood of spatial and temporal summation of aberrant depolarizations. Although at first glance similar to wakefulness, recent connectivity studies demonstrate a further strategic loss of connectivity in REM sleep which we hypothesize accounts for its unique antiepileptic influence on seizures.

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Review Article

Influence of Sleep and Sleep Deprivation on Ictal and Interictal Epileptiform Activity

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Sleep is probably one of the most important physiological factors implicated both in epileptic seizures and interictal epileptiform discharges. The neurophysiology concerning the relationship between sleep and epilepsy is well described in the literature; however, the pathological events that culminate in the seizures are poorly explored. The present paper intends to make a rigorous approach to the main mechanisms involved in this reciprocal relation. Knowledge of sleep and sleep deprivation effects in epilepsy stands as crucial in the understanding of how seizures are produced, their possible lines of treatment, and future research.

1. Introduction

There is a very important interaction between epilepsy and sleep. This connection is not new; since antiquity, it has been recognized that some seizures only appear during sleep, as a result of which they acquired magical significance. Hippocrates stated that a person affected with epilepsy should *"spend the day awake and the night asleep. If this habit be disturbed, it is not so good . . . worse of all when he sleeps neither night nor day"* [1].

Sleep and sleep deprivation have an influence in the onset, frequency, and semiology of seizures, as well as in EEG findings. Some seizure types have different circadian distributions, and understanding these patterns may provide useful diagnostic clues [2]. In 1885, Gowers observed in 850 institutionalized patients that 21% of seizures occurred exclusively at night, 42% only during day, and 37% interchangeably during day or night. In those terms, he classified seizures occurrence as diurnal, nocturnal and diffuse [3]. In 1890 Féré studied the times when the seizures occurred over 3 months in epileptic hospitalized patients, finding that two thirds all of seizures occurred between 8 p.m. and 8 p.m. [4]. Some years later, Langdon-Down and Russell Brain in 1929 analysed 2524 seizures in 66 patients over 6 months: 24% of seizures were nocturnal, 43% daily and 33% occurred randomly [5]. Janz was the first to describe what he called "awakening epilepsy." In 1969, he published five articles about the chronobiology of tonic-clonic generalized seizures in 2825 patients: 44% had seizures during sleep and 33% during waking [6]. Gibberd and Bateson studied 645 patients with epilepsy, founding that sleep-related epilepsy has an ultradian pattern differentiated at the beginning and end of sleep, while seizures in epilepsy daytime waking occur preferentially in the midafternoon [7].

The interaction between sleep and epilepsy is reciprocal; sleep affects the presentation mode of epilepsy and epileptic seizures modifies the sleep pattern and contributes to its fragmentation. Sleep deprivation is not only associated with epilepsy [8]. It has been implicated in several physiopathological effects, including decreased appetite, altered memory, and learning [9, 10]. Although there is abundant evidence that sleep deprivation facilitates the onset of epileptic seizures and interictal epileptiform discharges, there are also studies that propose a critical view of this claim arguing that sleep deprivation rarely occurs isolated but is in fact frequently associated with stress, alcohol, and so forth [11, 12].

The discovery and use of the electroencephalograph revolutionized the understanding of the relationship between epilepsy and sleep. Interictal epileptiform discharges are more common in NREM sleep [13]. The frequency of epileptiform discharges during sleep not only increases, but also affects their morphology and distribution [14]. There are several

partial and generalized epileptic syndromes associated with sleep. Recognizing them is essential in order to make an accurate diagnosis and suggest the adequate treatment.

2. Physiopathological Fundamentals

There is no clear explanation of the relationship between some types of epilepsy and its presentation during drowsiness, sleep, or awakening. Both sleep and some generalized seizure types share common neuroanatomical elements comprising the ascending reticular activating system, limbic system, and specific thalamic nuclei. *In vitro* electrophysiologic studies of human brain slices have reported that spontaneous activity and responses to synaptic activation in neocortex and hippocampal neurons differ in normal and epileptic tissues [15].

It is well accepted that both partial and generalized interictal epileptiform discharges increase during NREM (Non Rapid Eye Movement) sleep, whereas REM (Rapid Eye Movement) sleep suppresses generalized epileptiform discharges and shows variable effects on focal discharges. Sato and Nakashima reported that hippocampus-kindled cats showed a lower electroconvulsive seizure threshold in slow-wave sleep compared with wakefulness and REM sleep [16]. The synchronous oscillations of neurons generating cortical sleep spindles, K-complexes, and slow waves during NREM sleep promote the propagation of epileptic discharges. These could be some of the most important mechanisms involved in the trigger of seizures during NREM sleep. Therefore, epileptic discharges could appear instead of sleep spindles in a cortical response to intrinsic thalamocortical inputs [17]. In fact, the relation between sleep spindles production and epileptic activity has been documented. Frontocentral areas are the most important side of spindles production and, because of the rich interconnectivity between each region of the frontal lobe, sleep may facilitate motor seizures and other types of frontal seizures.

On the other hand, REM sleep is defined by the EEG desynchronization and loss of muscle tone. The EEG desynchronization prevents the spread of seizures during REM sleep as in wakefulness, and the lack of muscle tone blocks clinical expression of seizures. During REM in humans and other mammalians', sleep there exists an increasing GABAergic activity which is protective of seizures [18]. Therefore, seizures during this stage occur infrequently. The protective role of REM sleep is probably mediated by GABA hypothesis and other factors, such as the desynchronization pattern and reduced muscular tonus during this sleep phase. EEG recordings generally show absence or decreased epileptiform activity in most patients.

Biochemical changes responsible for cerebral hypersynchrony present during certain stages of sleep may encourage propagation of discharges. As mentioned above, several mechanisms have been implicated in this processes such as loss of inhibition on some circuits or thalamocortical facilitation and propagation of epileptiform activity occurs possibly as subgroups of seizures originating in the frontal lobe. Autosomal dominant frontal epilepsy, characterized by nocturnal seizures, appears to be associated with a mutation of the A-4 subunit of the nicotinic acetyl receptor (CHNRA-4) [19]. Therefore, the participation of the acetylcholine system may be considered. Monoaminergic and cholinergic brainstem receptors reduce firing rates producing hyperpolarization in thalamocortical relay neurons, which is maximal in NREM stages 3 and 4 sleep. During REM sleep, cortical activation occurs when cholinergic brainstem afferents increase firing rates producing depolarisation in thalamo-cortical relay neurons [20, 21].

Sleep deprivation is also an important trigger that increases the interictal epileptiform activity, especially in the transition from wakefulness to light sleep whose action mechanism probably increases cortical excitability [22]. Transcranial magnetic stimulation studies have shown that sleep deprivation is associated with important changes in inhibition-facilitation balance in the primary motor cortex of normal subjects. Motor threshold probably reflects axon membrane excitability, because drugs act on voltage and frequency-dependent calcium and sodium channels modulate it. These modifications might have a connection with the background factors of the "activating" effects of sleep deprivation [23]. Some laboratory studies have implicated nitric oxide, as inhibitory substance of seizure, associating the action of some anticonvulsant for mediating this [24]. However, other studies place it as proconvulsant substance; as in experimental studies with genetic absence occurs at high concentrations, their concentration is high during some seizures and sleep [25]. In the present state of knowledge, the most accepted conclusion is that nitric oxide behaves as a neuromodulator with dual (proconvulsive or anticonvulsive) action [26].

As shown, there are multiple pathophysiological mechanisms linking sleep to epilepsy. Therefore, having a deep knowledge of the features involved in sleep is very essential for a proper understanding of the characteristics of this type of seizures.

3. Epilepsy and Circadian Rhythms

Knowledge about the circadian rhythm implication on epilepsy is relatively limited. Gaining knowledge into this factor is very important for a better understanding of the physiopathology of epilepsy and for its diagnosis and treatment. Circadian rhythms are endogenously mediated 24-hour cycles of physiological processes, including the sleep-wake cycle, hormone production, and core body temperature. These circadian rhythms are modulated by a biological clock located in suprachiasmatic nuclei. This and other anatomical structures such as retinohypothalamic tract or pineal gland are responsible for the circadian pacemaker (process C), which allows alertness during the subjective day, sleepiness during the subjective night, and an increase in sleepiness (process S), which depends on the prior time awake [27]. There are several interesting studies that show a direct relation between epilepsy and sleep-wake rhythm both in animals and humans. Studies with rats placed in constant darkness manifested spontaneous limbic seizures occurring in

Table 1: Results of some interesting studies that relate seizures location and most frequently time of day.

Author	Year	Number of patients	Number of seizures	Focus	Peak hour
Pavlova	2004	26	90	Temporal	15–19 h
				Extratemporal	19–23 h
Durazzo	2008	131	669	Occipital	16–19 h
				Frontal and Parietal	04–07 h
				Temporal	16–19 h and 07–10 h
Hofstra	2009	33	450	Temporal	11–17 h
				Parietal	17–23 h
				Frontal	23–05 h

a mediated circadian pattern [28]. In genetic terms, it has been shown that the loss of circadian PAR bZIP transcription factors in mice may produce epilepsy [29].

There are numerous examples about the association between sleep and seizures in some frontal lobe syndromes (e.g., autosomal dominant nocturnal frontal lobe epilepsy) and myoclonic seizures in juvenile myoclonic epilepsy which appear most likely after awakening in the morning. Pavlova et al. described 90 seizures in 26 patients founding an increased likelihood of seizures between 15:00 and 19:00 hours (temporal epilepsy) and another peak incidence between 19:00 and 23:00 hours (extratemporal epilepsy) [30]. In 2006, Pung and Schmitz studied the circadian rhythms of 20 patients with juvenile myoclonic epilepsy and 20 patients with temporal lobe epilepsy. They found very interesting differences in the circadian activity patterns of both groups. They observed that patients with juvenile myoclonic epilepsy seem to have a characteristic circadian rhythm similar to an extreme eveningness (staying up late, getting up later in the morning). However, patients with temporal lobe epilepsy could be defined as "morning types" [31]. Durazzo et al. (2008) reported on 669 seizures in 131 patients showing occipital seizures peaked between 16:00 and 19:00 hours, frontal and parietal lobe seizures peaked between 04:00 and 07:00 hours; mesial temporal lobe seizures showed two peaks (16:00–19:00 and 07:00–10:00) [32].

On the other hand, Hofstra et al. in 2009 presented 450 seizures in 33 patients explored with long-term intracranial EEG and video monitoring. Their results were temporal lobe seizures occurred preferentially between 11:00 and 17:00 hours, parietal lobe seizures between 17:00 and 23:00 hours, and frontal lobe seizures between 23:00 and 05:00 hours [33] (see Table 1). Analyzing the studies mentioned, we can see that seizures originated in the temporal, parietal, and occipital lobes tend to occur in the afternoon. Instead of those originating in the frontal lobe tend to occur during the night.

Other parameters like body temperature, heart rate, and hormonal levels have been studied and related to seizures [34]. Several authors have reported reduced heart rate variability in people with chronic epilepsy. Likewise, normal baseline levels of cortisol have been described with postictal elevations, or elevated baseline prolactin levels have been observed and levels may rise further after seizures [35].

As we have seen, several studies have indicated the interaction between circadian rhythms and epilepsy. The results discussed previously suggest that some physiological factors with a circadian distribution can influence the presentation of numerous types of seizures. We believe that their identification is very important in order to help prevent seizures by modifying these factors.

4. Sleep and Ictal-Interictal Epileptiform Activity

The trigger capacity of NREM sleep on seizures and interictal epileptiform abnormalities has been widely tested. By contrast, REM sleep has inhibitory properties. Passouant named REM sleep "anticonvulsant sleep" because of its general inhibitory effect of anomalies, both ictally and interictally [36]. This effect is characteristic in hypsarrhythmia and also the epileptiform activity of the Lennox-Gastaut syndrome. During this sleep, phase generalized tonic-clonic seizures never occur. However, when localized anomalies observed during REM sleep exist, there is a good correlation with the topographic area.

In 1947, E. L. Gibbs and F. A. Gibbs observed in 500 patients that while 36% had interictal epileptiform discharges during awakening, 82% did so during sleep. They checked sleep-actives-independent foci in some patients, and the probability of interictal epileptiform discharges was highest in patients with acute psychomotor seizures [37]. Few years later, Gloor et al. observed in 300 patients that 57% had more interictal epileptiform discharges during sleep [38]. In 1972, Niedermeyer and Rocca reported that around 30% of patients with refractory temporal lobe epilepsy had interictal epileptiform discharges only during sleep. In these patients EEG is characterized by an increased frequency of spikes at sleep onset, being highest during slow sleep and decreasing in REM [39]. Frontal lobe seizures begin during sleep more frequently than temporal lobe seizures.

NREM sleep not only increases focal discharges. It also increases generalized discharges. In idiopathic generalized epilepsies, sleep increases the number of seizures and interictal epileptiform discharges. The spikes frequency increases when sleep starts and during slow sleep, decaying in REM sleep. The most common interictal abnormality in these patients are spike-wave discharges of 4 to 5 Hz; generalized short bursts of 1 to 3 seconds sleep duration, but more frequent drowsiness. In the same line, awakening is also

another physiological inductor, especially epilepsy with generalized tonic-clonic seizures and myoclonic epilepsies. The same can be said of the transition states between NREM and REM sleep, which are activators in epilepsy with generalized tonic-clonic seizures, myoclonic epilepsy, and absences. Sleep increases epileptic discharges in absences in 81–90% approximately. The spike-wave discharges at 3 Hz with continuous discharges during status are fragmented during NREM sleep. In the absence status, spike discharges and polyspike-wave can be seen isolated [40, 41].

In conclusion, analyzing the contributions of the authors consulted, NREM sleep has a pronounced trigger effect on different types of seizures and over interictal epileptiform discharges fundamentally secondary generalization of partial seizures, especially those of temporal lobe origin. During sleep, frontal lobe seizures occur more often than temporal lobe seizures. We believe that these are important reasons to include a period of sleep in routine EEG obtaining an increase in the diagnostic value and sensibility.

5. Sleep Deprivation and Ictal-Interictal Epileptiform Activity

The effects of sleep deprivation are known since long ago. The actions over cognitive and psychomotor functions, decreasing the concentration and attention, are known for all of us. If deprivation persists, diplopia, dysarthria, postural tremor, and psychotic symptoms occur. The relationship between sleep deprivation and epilepsy is very close. Malow said "Study of the effects of sleep deprivation on epilepsy may create a window of opportunity that could help decipher how seizures are triggered and facilitated, potentially providing an avenue for future interventions" [42].

Substantial evidence recognizes sleep deprivation as a precipitant of seizures. Sleep deprivation is used in some types of epilepsy to facilitate seizures for the diagnosis or presurgical evaluation of epilepsy. Sleep deprivation can promote and facilitate both seizures and interictal epileptiform discharges. It can detect epileptiform abnormalities in 35% of patients with normal EEG. This effect is especially evident in primary generalized epilepsy, independent of sleep effect [43–45].

There are several studies to support this thesis both in animals and humans. For example, in cats, sleep deprivation facilitates penicillin-induced seizures, and in one genetic model of absence epilepsy in rats deprived of sleep for 12 hours recorded an increased number of spike-wave discharges within first 4 hours of sleep deprivation [46, 47]. In 1962, Janz reported that sleep deprivation by alcohol-precipitated tonic-clonic generalized seizures, particularly after awakening [48]. Three years later, Mattson et al. published the following study: sleep-deprived EEGs were realized after 26 to 28 hours of wakefulness in 89 patients with a history of at least one seizure and a normal routine EEG, 34 patients with convulsive epilepsy and interictal epileptiform discharges on routine EEG, and 20 patients with other neurologic disorders (nonepileptic disorders). Interictal epileptiform abnormalities were recorded in 34%, 56%, and 0% of subjects, respectively [49].

During the 60s and the 70s, several studies in pilots and soldiers sleep deprived for long periods showed that seizures indeed occurred in the context of sleep deprivation but frequently associated with other factors such as stress, fatigue, alcohol, and drug abuse. In 1991, R. Degen and H. E. Degen compared the effect of total sleep deprivation on the EEGs of patients with different types of epilepsies. For most seizure types, spontaneous sleep and sleep-deprived recordings produced similar activation rates. Seizures were more likely to be activated by sleep or sleep deprivation in patients with idiopathic generalized epilepsy than partial epilepsy [50]. Two years later, Rajna and Veres observed that night sleep duration was directly correlated with seizures frequency in 14 patients with temporal lobe epilepsy. They saw that the probability of a seizure was significantly higher after a night of sleep deprivation compared with normal sleep [51].

A deep debate exists about whether the interictal epileptiform discharges activation produced by total sleep deprivation is due to sleep itself or because total sleep deprivation makes an independent activating effect. Some studies have proposed that total sleep deprivation does not offer greater activation than sleep alone; others claim that total sleep deprivation activates interictal epileptiform discharges independent of sleep induction. Rowan et al. described a significantly greater interictal epileptiform discharges yield following total sleep deprivation compared with routine wake; interictal epileptiform discharges were registered in 28% of the patients only following total sleep deprivation, and total sleep deprivation activated a new epileptic focus in 7% of cases [52]. In 2000, Roupakiotis et al. presented a study of 721 subjects who had a second EEG (routine EEG, drug-induced sleep, or total sleep deprivation) after an inconclusive basal EEG founding a significantly greater percentage containing interictal epileptiform discharges after total sleep deprivation as compared with a second routine record (22.6% versus 9.5%) [53].

As a finding, in line with Foldvary-Schaefer and Grigg-Damberger, we can say that comparative studies largely confirm that total sleep deprivation activates ictal and interictal epileptiform discharges in 23–93% of patients with definite or suspected seizures [54]. In our experience, partial sleep deprivation is useful for EEG routine producing a significant increase on epileptiform findings.

6. Sleep-Related Epileptic Syndromes

There are certain epileptic syndromes whose EEG abnormalities occur predominantly during sleep and which are clearly influenced by it. Fundamentally, there are partial epilepsies, which may be idiopathic, symptomatic, or cryptogenic. New diagnostic methods such as functional MRI, MRI with spectroscopy, and the tractography, and the introduction of the new antiepileptic drugs (e.g., Rufinamide in Lennox-Gastaut syndrome) have enabled innovative positions in the management of these diseases. The most important sleep-related epileptic syndromes are briefly described later.

6.1. Benign Childhood Epilepsy with Centrotemporal Spikes (BCECTS). This is the most common epileptic syndrome in

infancy and it can be considered a sleep-related epilepsy because 75% of all seizures occur exclusively during NREM sleep, being particularly frequent in the first third of the night [55, 56]. In nocturnal seizures, the generalization of the seizure often occurs. The EEG is usually normal during wakefulness (only 10–20% of all patients have seizures during wakefulness) and often during N1 and N2 sleep it shows abundant spikes or spike-wave localized unilaterally or bilaterally on the middle temporal and central regions. During N3, this activity tends to be multifocal, even generalized and, in some cases, when atypical evolution exists, a pattern similar to epilepsy with continuous spike-wave during slow sleep (less than 85% total NREM sleep) can be observed. During REM sleep the frequency, amplitude, and persistence of abnormalities decrease [57, 58].

6.2. Benign Childhood Epilepsy with Occipital Paroxysms. Childhood epilepsy with occipital paroxysms, which are blocked by the eye opening in waking, is clearly another syndrome facilitated by sleep, during which, in all phases, the presence of the paroxysms clearly increases. This facilitator feature and normality sleep architecture are different characteristics of occipital epilepsies and have a predictive value of benignity [59].

6.3. Frontal Lobe Epilepsy. Frontal lobe epilepsy usually presents seizures almost exclusively during sleep [60]. It is very important to make a correct differential diagnosis with certain parasomnias. EEG findings are crucial. Seizures originated in frontal lobe have some typical characteristics: predominant motor activity during event, short duration, minimal postictal confusion, and tendency to occur several times during the night. The most accepted thesis is that during sleep there is facilitation of frontal discharges in thalamocortical circuits, sometimes associated with sleep spindles and generated in thalamic nuclei [61]. Autosomal dominant nocturnal frontal epilepsy is expressed by a variety of clinical manifestations ranging from abrupt awakenings or dystonic movements, to complex motor behavior. Seizures are brief and usually occur in N2 sleep stage. The sleep architecture is normal. In some cases, there are anomalies described in "alternating cyclic pattern" [62, 63].

6.4. West Syndrome. West syndrome is a rare epileptic syndrome in infants. The epileptic seizures which can be observed are known as infantile spasms and EEG findings show a pattern described as hypsarrhythmia. The hypsarrhythmia shows a variation during sleep with typical EEG with multifocal spikes and high-voltage waves superimposed on a disorganized and chaotic baseline activity. During NREM sleep, amplitude increases basal activity and spike-wave discharges tend to cluster in periodic complexes. In REM sleep, epileptiform activity decreases or disappears [25].

6.5. Landau-Kleffner Syndrome. This syndrome is characterized by seizures initially of easy control and sensory aphasia. The EEG shows epileptiform discharges which are highest in temporal or central temporal areas. During NREM sleep these discharges tend to be continuous and disappear or be fragmented during REM sleep [64]. In the Landau-Kleffner syndrome basal EEG activity can be normal during wakefulness and find continuous spike-wave discharges during sleep. It is believed that the epileptic discharges during sleep are facilitated by the spindles.

6.6. Lennox-Gastaut Syndrome. Lennox-Gastaut syndrome is an epileptic encephalopathy characterized by different seizure types and increasing abnormal activity during sleep. The average age of onset is between 2 and 5 years. It is characterized by difficulty to control seizures being tonic and atonic as the most frequent. In most cases, there is a variable degree of mental retardation. Approximately half of the patients have a significant perinatal history of intraventricular haemorrhage, neuronal migration disorder, Aicardi syndrome, tuberous sclerosis, or West syndrome. The EEG characteristically shows multifocal, diffused or generalized discharges of slow spike-wave or polyspike wave. During sleep polyspike activity can be prominent and basal activity can be seen as continuous epileptiform activity. Rhythmic activity of 10 to 25 Hz occurs almost exclusively during sleep [65]. However, the only seizures consistently promoted during sleep are tonic seizures. The increased activity during sleep is associated with poorer clinical prognosis.

6.7. Epilepsy with Continuous Spike-Wave during Slow Sleep. This type occurs in children. Often these patients have some degree of mental retardation and/or learning difficulty. EEG findings may have multifocal discharges. Typically, the EEG during NREM sleep slows epileptiform discharges with maximal amplitude in frontal areas and continuous activity of spike-wave which fills approximately 85% of the record [66].

6.8. Juvenile Myoclonic Epilepsy. Juvenile myoclonic epilepsy is the most common generalized epilepsy primarily in adolescents and adults. It is characterized by myoclonic jerks (in all patients) and other type of seizures (generalized tonic-clonic, absences, etc.). The seizures occur preferentially after awakening and are very sensitive to sleep deprivation, alcohol, or photostimulation. Interictal activity is short bursts of polyspikes and polyspike-wave complexes after spontaneous or induced awakenings [67, 68]. In general, sleep architecture is affected, with decreased quality and sleep fragmentation.

6.9. Epilepsy with Generalized Tonic-Clonic on Awakening. In 1885, Gowers described a group of patients whose seizures appeared after waking. Epilepsy with generalized tonic-clonic on awakening has many similarities with juvenile myoclonic epilepsy as to the age of onset or precipitating seizure factors. 90% of all seizures occur within 2 hours following waking, at any time of day. Most frequently, interictal anomalies are generalized spike-wave or polyspike-wave complexes, arrhythmic, of a few seconds of duration, with frequencies of about 3 to 6 Hz. This activity is facilitated by hyperventilation, sleep deprivation, and photostimulation [69].

7. Conclusions

Despite the clear relationship between sleep, sleep deprivation, and epilepsy, we know little about it. The most accepted thesis suggests that the relationship is reciprocal and that overall both conditions (sleep and sleep deprivation) have an excitatory effect on certain types of epilepsy. The tendency to circadian presentation of some epileptic syndromes and the trigger effect of NREM sleep on epileptic seizures are good examples. However, some authors question these claims, particularly those related to the effect of sleep deprivation on epilepsy. Moreover, treatment of these sleep disorders can lead to improved seizure control.

Correct understanding of issues like the process of genesis and propagation of the seizures, or sleep-related epileptic syndromes is crucial in order to make a correct diagnosis and appropriate treatment.

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Review Article

Controversial Issues on EEG after Sleep Deprivation for the Diagnosis of Epilepsy

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EEG after sleep deprivation (SD-EEG) is widely used in many epilepsy centers as an important tool in the epilepsy diagnosis process. However, after more than 40 years of use, there are a number of issues which still need to be clarified concerning its features and role. In particular, the many scientific papers addressing its role in epilepsy diagnosis often differ remarkably from each other in terms of the type of patients assessed, their description and study design. Furthermore, also the length and the type of EEG performed after SD, as well as the length of SD itself, vary dramatically from one study to another. In this paper we shortly underscore the abovementioned differences among the different reports, as well as some interpretations of the findings obtained in the different studies. This analysis emphasizes, if needed, how SD-EEG still represents a crucial step in epilepsy diagnosis, and how additional, controlled studies might further shape its precise diagnostic/prognostic role.

1. Introduction

The relation between sleep and epilepsy had already been described in scientific papers still before the use of EEG [1], and the role of sleep deprivation (SD) in promoting epileptic seizures and facilitating interictal epileptiform abnormalities (IIAs) has been studied since the 60s [2].

EEG after sleep deprivation (SD-EEG) was thus proposed as a method to increase the yield of EEG in revealing IIAs in patients with suspected seizures and to further improve the accuracy of the diagnosis of epilepsy. Several experimental studies in animal models, healthy controls, and epileptic patients highlight the role of SD and sleeping during an inappropriate circadian phase (i.e., in the morning) in enhancing sleep instability and possibly causing the occurrence of IIAs [3]. Moreover, SD enhances cortical excitability in patients with different subtypes of epilepsy more than in controls [4]. These pathophysiological issues are beyond the aim of this paper, in which we would rather focus on several controversial issues that make the interpretation of findings obtained by SD-EEG difficult even after more than 40 years of its use.

2. Variability in SD-EEG Protocol and Examined Population

The results of published SD-EEG studies testing this method are difficult to compare to each other, mainly because of the protocols used and the population of patients assessed. Concerning the first issue, the protocol of SD (total or partial), the length of the SD-EEG recording, the recording of drug-induced sleep, and the time of the day of the recording (morning or afternoon) constitute the main variables. Moreover, the inclusion and exclusion criteria in the published papers are very different concerning age (children versus adults), seizure and epilepsy types, absence of abnormalities on basal

EEG, neuroimaging, and treatment with antiepileptic drugs (AEDs). Again, even the definition of epileptic IIAs is not homogenous and, last but not least, most of the studies are retrospective, using Epilepsy Center databases.

The protocol of SD (i.e., SD lasting at least 24 h, or partial SD) varies significantly in the different studies. In most of the earlier reports, the authors induced at least 24 h SD, while, more recently, several groups started testing the effects of partial SD (see, e.g., [5–9]) with lengths of sleep allowed during the night before SD-EEG varying from 3 h [8] up to 7 h [6].

Interestingly, almost unanimously in studies on children, authors use age-related partial SD, increasing with patients' age [5, 6, 8, 10–15], and since such duration also varies significantly from one study to another, this represents another confounding factor for interpreting its role for epilepsy diagnosis.

Also, *the duration of EEG recordings*, which is a potentially critical issue for IIAs yield (see below), varies significantly among different centers, ranging from 30 minutes [16] up to even 24 h [17]; further, in some studies authors include, during SD-EEG recordings, also hyperventilation and intermittent photic stimulation, while others do not (see below).

The *time of the day of the recording* (morning, afternoon, or night) is related to different circadian rhythms and mechanisms of sleep (see as a review [18]) and possibly to a different risk of occurrence of IIAs in different types of epilepsy.

Apart from basal EEG and SD-EEG, in the same study, some authors performed also a further EEG during *sleep induced by hypnotic drugs*, such as promazine, barbiturates, or benzodiazepines [19–22].

The last issue to be considered concerning SD protocol is the *interval* between the last suspected seizure and the SD-EEG recording. A residual postictal activation seems to be likely only when performing SD-EEG within 2-3 days after seizure [6, 23], but in the routine clinical practice this rarely occurs, and thus it is not as important as expected [9].

Another major issue varying from one study to another is the *population* studied. Even though the majority of the studies recruited patients undergoing a complete evaluation for suspected epilepsy, other inclusion and exclusion criteria are often not comparable, and in many cases it is not even possible to separate and analyze single variables.

In fact, only few prospective series have been published [11, 14, 22, 24–27], while most studies are retrospective using data from Epilepsy Center databases.

Even though age is considered critical for SD-EEG outcome, in some reports both adults and children have been included in the same group [5, 6, 8, 10, 16, 21, 24, 25, 28–34]. Moreover, although occurrence of *IIA during the first routine wake EEG* could be considered as an exclusion criterion in studies testing SD-EEG sensitivity, this aspect is sometimes not evaluated or not considered as a bias (see, e.g., [6, 10, 11, 15, 16, 20, 29, 33, 35]).

Concerning the *classification of epilepsy*, the oldest studies included patients with different types of seizure or syndrome, which were often only roughly classified [6, 10, 22, 24, 25, 28, 31, 32, 34, 36–39], while some of the newer ones included populations more homogeneous concerning those aspects [16, 17, 40–44]. In some papers, epilepsy/seizures classification and other clinical features are not even clearly specified (see [5, 7, 8, 11, 21, 33, 45, 46]).

Therapy with AEDs is another aspect varying from one study to another. Only in a few studies SD-EEGs were performed in *de novo* patients which had never been treated with AEDs [6, 8, 9, 14, 20, 23], while in most of the remaining ones, also patients taking AEDs were included, and therapy was left unchanged or at least AEDs tapering was performed thus probably significantly affecting occurrence of IIA and, thus, sensitivity and specificity of SD-EEG [47–49]. Furthermore, the number and type of AEDs were not described in detail in most papers (see, e.g., [10, 11, 13, 15, 16, 22, 24, 25, 27, 31, 32, 34, 40, 42, 44]), with some exceptions [17, 41, 46].

Another critical issue is the *definition of IIAs,* since usually EEG activation was defined by the occurrence of specific epileptic IIAs, but in some studies the authors considered also occurrence of slow waves [11, 12, 20, 23, 29], and, in a surprisingly high number of studies, the types of EEG abnormalities were not even specified [13, 21, 26, 32, 33, 38, 39].

Several epilepsy syndromes (especially IGE, but also some focal ones) often show a photoparoxysmal/photoconvulsive response to intermittent light stimulation performed during EEG. The potentiation/unveiling of such an effect might occur after SD thus significantly helping in the diagnosis. Unfortunately, even in the few SD-EEG studies including such a protocol, a detailed analysis of the results was not reported, or, when IIAs occurrence during photic stimulation was listed, a correlation with seizure type(s) or syndrome was not provided (see, e.g., [21, 22, 37]).

3. Interpreting the Role of SD-EEG in Epilepsy: Does SD Effect Exist?

Two important questions about the role of SD in inducing IIAs and thus in the diagnostics process of epilepsy are (1) whether the increased sensitivity of SD-EEG is due just to an effect of sampling or length of the recording, and (2) whether sleep *per se* or rather SD, indeed, induces activation of the EEG.

Concerning the first issue, some authors hypothesized that the occurrence of IIAs during SD-EEG is due just to a sampling effect related to a second EEG [22], since it is known that the sensitivity of EEG increases proportionally to the number of repeated routine EEGs [50–52]. However, the papers analyzing the role of a second routine EEG in patients with IIAs during SD-EEG do not support this hypothesis.

Three studies, back in the 60s, showed that only a very small percentage of patients (<20%) with IIAs during SD protocol presented also an abnormal second routine EEG [24, 25, 36]. Recently, our group found retrospectively that, among 61 epileptic patients bearing a basal normal/nonspecific EEG, a second routine EEG revealed IIAs in 13.1%, while IIAs occurred in 45.9% of their SD-EEG [9]. In an elegant prospective study [20], SD-EEG was more likely to show epileptiform discharges as compared to routine EEG, SD-EEG, and drug-induced sleep EEG, performed in random order.

The duration of SD-EEG recording should be also considered, since SD-EEG recording lasts usually much longer than basal EEG. Even though there is no formal study on this issue,

in the general experience, IIAs occur also during the first part of SD-EEG and the sensitivity of SD-EEG is similar in studies using different durations of recordings [9, 39].

Another debated aspect is whether sleep *per se* or SD induces EEG activation. Apart from physiological speculations, current data have to be considered as not definitive, and the provocative effects of both SD and sleep/drowsiness are likely to enhance each other.

Some data suggested that EEG activation is already present during the waking phases of EEG recorded after SD [15, 24, 25, 30–32, 37, 40, 42]. However, in most cases, epileptiform discharges occurred more frequently during sleep [11, 14, 46], in particular during light sleep stages [8, 9, 19, 22, 23]. Some exceptions exist in which IIAs occurred both during wakefulness and sleep [5, 34, 35, 37].

When directly compared to each other, spontaneous sleep seemed to increase significantly generalized discharges, while sleep occurring after SD might increase more focal discharges [39]. On the other hand, the comparison between SD-induced sleep and drug-induced sleep gave discordant results. Four studies [16, 32, 35, 40] showed a similar yield in IIAs occurrence between the two approaches, while the other three ones [20–22] found a significantly higher activation rate in SD-EEG.

4. Sensitivity and Specificity of SD-EEG in Epilepsy and in Different Syndromes

Given the dramatic differences highlighted above, the variability of sensitivity and specificity in single studies is not surprising. In fact, the occurrence of IIAs during SD-EEG ranges from 20% [42] to 57% [45] in adult patients with the diagnosis of epilepsy, and between 32% [36] and 54% [30] in children.

Some features of epilepsy seem to be more likely to be associated with IIAs occurrence during SD: activation seems to be greater shortly after epilepsy onset or seizures occurrence [23, 25, 31, 40], in patients with an earlier seizure onset [19], and in those with a history of recurrent seizures [15, 23].

Concerning the role of different types of syndrome or seizures, the first observation, by Mattson et al. [24], reported a slightly higher activation rate in patients with "grand mal" seizures, than in those with "psychomotor" seizures, and few years later, Pratt et al. [25] found SD EEG activation in 41% of patients with grand mal seizures, 47% of psychomotor seizures, and 37% of other focal seizures. The main limit of these studies was the lack, at that time, of an unanimously accepted seizure classification. In more recent observations, even though data are not consistent and numerous, we could state that, according to R. Degen and H.-E. Degen [16], activation is more frequent in patients with complex partial seizures only, as compared to complex partial seizures plus other seizures types. Gandelman-Marton and Theitler [23] did not find any activation in patients with focal seizures, while 29% of patients with focal seizures with secondary generalization and 20% of patients with primary generalized tonic-clonic seizures presented IIAs during SD. Concerning syndrome classification, a higher activation in idiopathic generalized epilepsy [9, 11] and in particular in awakening grand mal and childhood absence epilepsy [19, 32], has been reported.

Neuroimaging data were available for few patients only in few recent SD EEG casistics [6, 9, 10, 17, 23, 27, 39, 41, 44]. In most of them, the number of patients included was too low for allowing statistical correlations between specific size/site/nature of the lesions and neurophysiological data. Also, in our recent study [9], the diagnostic power for SD-EEG is not statistically different among subgroups of focal epilepsies. In the largest study [6] in 300 *de novo* patients, among which only those with a previous negative basal EEG underwent a SD-EEG, the authors found that 17% of patients with EEG diagnosis of partial epilepsy had abnormal CT/MRI.

Since the earliest studies on SD EEG, specificity has been assessed and shown to be very high. Back in the late 60s, two papers showed a specificity of 99 and 100% respectively [24, 36], and more recent papers showed similar results, thus confirming an occurrence of IIAs in 0 up to 12% of adult controls [27, 35]. Even more recently, in a retrospective study assessing the role of partial SD EEG in a wide population of patients assessed for suspected seizure, bearing a normal basal EEG and with a prolonged followup, we confirmed a high specificity rate (91.1%) [9].

5. Conclusions and Future Perspectives

Epilepsy is a complex disease, whose diagnosis is the results of the combination of anamnesis data and clinical history with diagnostic techniques, among which neuroimaging and EEG play a pivotal role. Actually, it is more appropriate to talk about epilepsies, rather than epilepsy, because different syndromes/seizure types differ markedly from each other, in terms of aetiology, pathophysiology, prognosis, and of appropriate treatment. An "ideal" diagnostic tool should be able to discriminate between epilepsy and non-epilepsy, that is, it should help to predict the likelihood of seizure recurrence in subjects experiencing a first seizure. The predictive value of the diagnostic exam is particularly crucial for epilepsy, especially in light of the burden of potential side effects of AEDs, which often need to be taken for years by patients, and of the stigma still surrounding the diagnosis of epilepsy. Thus, such a test should be very specific for epilepsy, and as sensitive as possible, in order to avoid the potential risk of not treating epileptic. As described above, SD-EEG has been generally shown to bear a high specificity, and seems to be, thus, a good diagnostic tool.

However, in the previous paragraphs we underscored the main difficulties in getting the full-blown potentiality of SD-EEG recording: these are mainly related to the huge methodological variability among the different studies in the field. Among them, the most relevant ones are represented by the striking differences in patients population and the SD-EEG protocols themselves, which often varies significantly from one centre to another. Furthermore, many of the most important studies on SD-EEG and epilepsy date back to several decades ago, when neuroimaging data on the patients were lacking (especially the nowadays routinely performed

MRI data) and some epilepsy syndromes subtypes had not been detailed yet.

An "ideal study" to clarify most of the abovementioned issues should include at least: (a) *de novo* potentially epileptic patients, in order to rule out the potential effects of AEDs on SD-EEG sensitivity; (b) data concerning multiple routine EEGs and SD-EEG for each patient, in order to test directly the role of the sampling effect on the diagnostic yield of SD-EEG; (c) a comparison of different lengths of SD and EEG recording, in order to help selecting the protocol with the highest potential compliance; (d) for each EEG recording (either basal or after SD) the occurrence of IIAs during the wake period, in order to clarify the role of sleep *per se* versus a specific role of SD; (e) performing additional stimulation, such as intermittent light stimulation, to address the effect of SD on its IIAs yield; (f) for each patient, an adequate followup in order to detail the occurrence of epileptic seizures, that is, the diagnosis of epilepsy. Of course, a prospective approach and an adequate amount of patients would be preferable; in any case, the detailed analysis of EEG IIAs occurrence should be performed by investigators rigidly blinded to the final diagnosis (i.e., epilepsy or not epilepsy) and features of the patients. The latter is a key requisite for avoiding the potential bias of over interpreting the role of a technique which, by itself, is considered crucial for the diagnosis itself, and is difficult to be ruled out in most of the existing studies on SD-EEG, which are retrospective in nature.

A study bearing all of the features as above is, of course, impossible to be performed. However, it would be already important to have studies fulfilling at least some of the above-quoted features; these should be multicenter to recruit as many patients as possible.

In conclusion, the history of the role of SD-EEG in epilepsy is still far from being fully elucidated, and many results suggest that this approach should not be considered *âgée*, but rather still one of the most useful diagnostic tools in the hands of epileptologists for many more years.

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