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Relationship between location of epileptic focus and occurrence during sleep versus wakefulness

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ABSTRACT

Objective. Different sleep stages exert differential effects on interictal discharges, neural synchrony and seizure threshold. We sought to assess the relationship between localization of the epileptogenic focus and seizure distribution in sleep versus wakefulness among patients with refractory epilepsy.

Methods. We conducted a retrospective chart review-based study. Video-electroencephalography of patients with refractory epilepsy, planned for resective surgery, were reviewed for seizure localisation and occurrence relative to stage of sleep/wakefulness. Demographic/clinical data, including details of surgery, were also recorded. Bivariate analysis was conducted using the chi-square test for proportions and unpaired t-test/ANOVA to compare the means within groups.

Results. We enrolled 175 patients (107 males) with a mean age of 26.1 ± 9.8 years (range: 4-53 years). We analysed 1,282 seizures, of which 916 (71.5%) were temporal, 95 (7.4%) frontal, 144 (11.2 %) central/ parietal and 19 (1.5%) arose from the occipital lobe. Temporal lobe onset seizures were more frequent during wakefulness (77.7%) compared to extra-temporal localization (65%) (p<0.0001). Amongst temporal lobe onset seizures, those during wakefulness arose more frequently from the lateral temporal (88.6%) compared to the mesial temporal lobe (75.5%) (p=0.0003). A higher proportion of seizures evolved into secondary generalisation during sleep (23.5%) versus 8.7% during wakefulness (p<0.0001).

Significance. Our study demonstrates that lobar location of epileptogenic foci is associated with a predilection of seizures to occur, as well as secondarily generalise, during sleep/wakefulness. Seizures with lateral temporal lobe as well as extratemporal lobe onset were more likely to occur during wakefulness. Overall, sleep related seizures were more likely to be of extratemporal lobe onset, though.

Key words: focal epilepsy, refractory epilepsy, sleep cycle, temporal, extratemporal

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Epilepsy and sleep share a complex yet fascinating relationship, with various sleep stages exerting differential influences on the occurrence of interictal discharges and seizures, as well as neuronal synchrony [1, 2]. Non-rapid eye movement (NREM) sleep, particularly Stage 2 NREM, facilitates focal seizures, whereas rapid eye movement (REM) sleep is known to inhibit them [3-5]. More than a third of focal seizures arise in sleep, usually in Stage 1 or 2 of NREM sleep. Moreover, sleep-related focal seizures have a higher likelihood of generalising compared to focal seizures occurring during wakefulness. The thalamocortical circuitry, which is responsible for hypersynchrony during NREM sleep and the generation of sleep spindles as well as delta activity, may also facilitate epileptic foci. It is well known that REM stage-related desynchronization imparts protection against the occurrence of focal seizures, as well as propagation in temporal lobe epilepsy (TLE) [6]. Additionally, some patients may have seizures only during sleep, and most purely sleep-onset seizures tend to be focal at onset [7].

Sleep may also have important connotations for presurgical evaluation in drug-refractory epilepsy; seizures arising during wakefulness may yield a different localization from those recorded during sleep. The lobar location from which a seizure emanates is also influenced by the sleep-wake cycle. Focal seizures of frontal origin are known to occur more commonly in sleep compared to seizures of temporal lobe origin [6, 8]. This may also have long-term implications as focal seizures that occur exclusively in sleep may portend poorer prognosis than generalised seizures occurring only in sleep, with poor seizure control, medical intractability and greater propensity for development of seizures during wakefulness [9]. The localising and lateralising value of sleep/awake state on seizures in patients with drug-refractory epilepsy has also been previously demonstrated [10, 11].

We hypothesized that information gleaned from the relationship between sleep/awake stage and focal seizures would contribute towards better understanding of localization in patients with drug-refractory epilepsy, with non-localizing ictal and inter-ictal electroencephalography (EEG). The primary purpose of our study was to assess the relationship between localization of the epileptogenic focus and the distribution of seizures in sleep versus awake states. The secondary objectives were to document the relationship between seizures and stage of sleep, and to compare the frequency of secondary generalisation during wakefulness versus sleep.

Materials and methods

We conducted a retrospective, chart review-based study, in which records of patients with drug-refractory epilepsy admitted under a single unit of the neurology department at our centre were reviewed and analysed. 'Drug-refractory epilepsy' was defined as per the International League Against Epilepsy definition as failure of an adequate trial of two appropriate and tolerated antiepileptic drugs in controlling seizures [12]. Records between January 2012 to January 2017 were reviewed. Of these, records of patients with focal epilepsy who had been discussed in our comprehensive refractory epilepsy patient management meetings and planned for resective surgery (that is, proposed lobar/sub-lobar of resection was determined) were selected. Patients with only non-epileptic events recorded on video-EEG, and those with clear features of generalized epilepsy were excluded. In addition, patients in whom more than one epileptogenic focus was suspected or those with unclear single focus were excluded. The study was approved by the institutional ethics committee.

Video-EEG records were obtained from the EEG laboratory where the data remains archived after patients are discharged from the epilepsy monitoring unit (EMU). Demographic and clinical details, as well as details of evaluation performed, were collected. In addition, for the subset of patients who had undergone resective epilepsy surgery, additional data regarding type of surgery, duration of epilepsy prior to surgery, age at the time of surgery, immediate complications in the post-operative period and post-surgical seizure outcome were also recorded.

Long-term scalp video-EEG recordings, conducted using the 10-20 international system (with additional anterior temporal electrodes placed for all patients) were reviewed by the neurology researcher (PN) for ictal (clinical plus EEG) as well as interictal evidence of localization. This researcher was blinded to the analysis and localization made by a senior epileptologist and sleep specialist (GS). All recorded seizures were studied and localisation of every seizure determined individually. In case of inter-rater disagreement, a re-review was carried out and final localization was established by consensus. Localization of video-EEG was made based on clinical, ictal and interictal data. Concordance was assessed between clinical and EEG findings for all seizures. Determination of state of seizure occurrence (awake, NREM stages [N1, N2, N3] and REM) was made. For this purpose, sleep stage scoring was conducted independently by GS. Characterisation of the sleep states was made on the basis of EEG features and eye movements, as recorded over fronto-polar channels.

Localization of the possible epileptogenic focus for individual patients was noted. This was based on the consensus reached during our comprehensive patient management meetings for epilepsy surgery, through a review of video-EEG, epilepsy protocol 3 Tesla brain

MRI, positron emission tomography (PET) brain, and SISCOS (subtraction ictal SPECT coregistered to interictal brain SPECT) or SISCOM (subtraction ictal SPECT coregistered to brain MRI) findings.

SISCOS was obtained for patients fulfilling any of the following broad criteria:<?show

- patients with extratemporal substrate on MRI and/or localisation on long-term video-EEG recording;
- patients with bilateral temporal lobe substrate on MRI and/or localisation on long-term video-EEG recording;
- localisation on video-EEG, non-concordant with imaging data;
- patients with normal MRI; and
- patients with previous epilepsy surgery.

FDG PET was obtained for patients with normal MRI, suspected dual aetiology, patients with previous epilepsy surgery, patients with focal cortical dysplasia other than type II and those with a wide field of localisation based on video-EEG. SISCOS and PET scans were also obtained if discussed as required, during our weekly patient management meetings.

In addition, all representative clinical, video-EEG and MRI data of individual patients were collated into Microsoft PowerPoint ® presentations for independent re-review by the epileptologist (GS).

Statistical analysis

Data were entered using Epi-Info version 3.5.4 and transferred to Microsoft Excel 2010. Results of descriptive analysis are presented as proportions with 95% confidence intervals or as mean (SD) or median (interquartile range [IQR]) wherever applicable. Bivariate analysis was performed using the Chi square test when variables were present as proportions. Unpaired t-test/ ANOVA was applied to compare the means within groups. Post-hoc test was applied when ANOVA was significant for groups showing significant difference in mean values. Statistical analysis was performed using Stata 11 software. *P* value of less than 0.05 was considered significant.

Results

We enrolled 175 patients (107 males, 68 females) with a mean age of 26.1 $\pm$ 9.8 years (range: 4-53 years). The mean age at onset was 11.3 $\pm$ 8.2 years. The mean duration of illness was 14.4 $\pm$ 8.1 years. Forty six patients (26.3%) reported a history of most of their seizures occurring during wakefulness while 12 (6.7%) reported their seizures occurring mostly during sleep. The commonest aetiology in our cohort was hippocampal sclerosis (HS) in 59 patients (33.7%) followed by focal cortical dysplasia (FCD) in 34 patients (19.4%) (*table 1*).

Ninety-two (52.5%) patients underwent epilepsy surgery and 83 (47.5%) had been selected for surgery following discussion at our patient management meetings at inclusion. Of the 92 operated patients, 67 (72.8%) were seizure-free in the post-operative period.

A total of 1,282 seizures were recorded during the video-EEG studies of these 175 patients. The median number of seizures per patient was 5 (IQR: 4-8). A total of 916 (71.5%) seizures were found to be of temporal lobe onset, 95 (7.4%) were frontal, 144 (11.2%) originating from the central/ parietal location and 19 (1.5%) arising from the occipital lobe (*table 2*). As clear parietal lobe onset was found in very few patients, these were grouped together with patients with central localisation. No localisation could be established in 108 (8.4%) seizures. A total of 332 (25.9%) of the 1,282 seizures occurred in sleep (*table 2*). Seizure onset was found most commonly during Stage 2 NREM sleep and no seizures were reported during REM sleep.

Temporal lobe seizures were more frequent during wakefulness (712/ 916, 77.7%) compared to seizures with extratemporal localization (238/366, 65%) ($p<0.0001$), including frontal lobe seizures ($p=0.003$) which were significantly more frequent during sleep. Among temporal lobe-onset seizures, 77.7% started during wakefulness and 19.5% in Stage N2 sleep. Of these, seizures during wakefulness occurred significantly more frequently from the lateral temporal lobe (88.6%) compared to those arising from the mesial temporal lobe (75.5%) ($p=0.0003$). Among frontal lobe seizures, 64.2% occurred in the awake state, while 35.8% occurred during sleep. All seizures arising from the occipital lobe occurred during wakefulness. Among seizures originating from the central/parietal region, 75% occurred in the awake state and 23.6% in Stage N2.

A significantly higher proportion of seizures evolved into secondary generalisation to a bilateral tonic-clonic state during sleep (78/332, 23.5%) compared to 8.7% of seizures during wakefulness (83/950) ($p<0.0001$). There was no significant difference in the rate of secondary generalisation among seizures occurring in different stages of NREM sleep (*table 3*).

A total of 15.5% temporal lobe seizures were found to evolve into secondary generalisation, while 5.3% of frontal lobe seizures were associated with secondary generalization. Temporal lobe seizures generalized much more frequently during sleep (35.8%) than during wakefulness (9.7%) ($p=0.0001$), as shown in *table 3*. No significant difference in secondary generalisation in sleep versus wakefulness was noted for frontal lobe ($p=0.246$) or central/parietal origin

▼ **Table 1.** Demographic and clinical characteristics of participants (*n*=175).

Parameters	Total (*n*=175)	Temporal (*n*=135)	Extra temporal (*n*=40)	*p* value
Age (years)	26.1 ± 9.7	26.9 ± 9.5	23.1 ± 10.3	0.03
Age at onset (years)	11.3 ± 8.2	11.8 ± 8.7	9.7 ± 6.4	0.156
Sex				
Male	107 (61.1)	82	25	0.84
Female	68 (38.9)	53	15	
Seizure frequency				
Daily	48 (27.4)	29 (21.4)	19(47.5)	
1-5/ week	34 (19.4)	25 (18.5)	8 (20)	0.019
1-3/ month	90 (51.4)	78 (57.7)	13 (32.5)	0.81
1-4/ 6 months	2 (1.1)	2 (1.4)	-	
1-2/ years	1 (0.6)	1 (0.7)	-	
Self-reported sleep/awake predilection				
Most seizures during wakefulness	46 (26.3)	39 (84.8)	7 (15.2)	0.245
Most seizures during sleep	12 (6.9)	7 (58.3)	5 (41.7)	
Most seizures upon awakening in the morning	3 (1.7)	2 (66.7)	1 (33.3)	
No predilection	114 (65.1)	87 (76.3)	27 (23.7)	
Precipitating factors				
Yes	4 (2.3)	3	1	0.918
No	171 (97.7)	132	39	
Radiological findings				
HS	59 (33.7)			
FCD	34 (19.4)			
DNET	13 (7.4)			
Tumour	2 (1.1)			
Gliosis	19 (10.9)			
MCD	3 (1.7)			
Others (cavernoma, calcification)	18 (10.3)			
Dual pathology	23 (13.1)			
Normal	4 (2.3)			

All values represented as frequency (%) or mean + SD. HS: hippocampal sclerosis; FCD: focal cortical dysplasia; DNET: dysembryoplastic neuroepithelial tumour; MCD: malformation of cortical development.

seizures (*p*=0.411). Seizures that appeared non-localizable on ictal video-EEG were found to be more frequently generalised during sleep than during wakefulness (*p*=0.048). The mean number of seizures was greater in the awake state, compared to sleep, irrespective of the underlying aetiology of focal epilepsy, and the occurrence of seizures during wakefulness/sleep was found to have no association with underlying aetiology (S1).

We also separately analysed 67 patients who had undergone epilepsy surgery and were seizure-free at one year of follow-up (S2). A total of 432 seizures were recorded in this subgroup (S3). Of these, 60.4% were of mesial temporal onset, 4.6% frontal and 3.9% each of parietal and occipital lobe onset. Seizures occurred predominantly in the awake state and 24.2% were found to arise in NREM sleep Stage 2 (S4). No seizure occurred in REM sleep. Among temporal lobe seizures, 71.5% occurred during wakefulness and 26% in NREM Stage 2. Among frontal lobe seizures, 31.1% occurred in sleep (all in NREM Stage 2). Similar to the overall group findings, secondary generalisation was slightly more common in the awake state (35/65; 53.8%). These findings distributed during sleep and wakefulness are similar to those observed in the entire group. However, contrary to the overall group findings, temporal lobe seizures generalised more frequently during wakefulness

▼ **Table 2.** Distribution of seizures in awake/sleep states according to lobe of origin.

Localization of seizures	Awake	N1	N2	N3	Total
Temporal	712 (77.7)	21(2.3)	179 (19.5)	4 (0.4)	916
Mesial temporal	572 (75.4)	17 (2.2)	165 (21.8)	4 (0.5)	758
Lateral temporal	140 (88.6)	4 (2.5)	14 (8.9)	-	158
Frontal	61 (64.2)	2 (2.1)	32 (33.7)	-	95
Occipital	19 (100)	-	-	-	19
Central/parietal	108 (75)	2 (1.4)	34 (23.6)	-	144
Non-localising	50 (46.3)	2 (1.9)	55 (50.9)	1 (0.9)	108
Total, *n* (%)	950	27	300	5	1282

(%) represents percentage of total seizures arising from that lobe

and frontal lobe seizures during sleep, although these numbers were small.

Discussion

The present study provides information on predilection of occurrence of seizures during sleep/awake states in patients with refractory focal epilepsy who had been selected for or had undergone epilepsy surgery, based on lobar location of epileptogenic foci. The study confirms some previous observations that NREM sleep, particularly Stage N2, facilitates focal seizures and REM sleep possibly plays an inhibitory role [1, 13-15]. Additionally, we demonstrate the differential propensity of seizures arising during sleep or wakefulness, depending on the lobe of origin. Findings in the subgroup of successful epilepsy surgery patients were similar to those of the entire cohort of patients included in this study.

▼ **Table 3.** Association between secondary generalisation of seizures and awake/sleep states or lobar origin.

State		Seizures with secondary generalisation (%)	Seizures without secondary generalisation (%)	*p* value
Awake state		83 (8.7)	867 (91.3)	<0.0001
N1		7 (25.9)	20 (74.1)	NS
N2		70 (23.3)	230 (76.7)	NS
N3		1(20.0)	4 (80.0)	NS
Source of seizure				
Temporal		142 (15.5)	774 (84.5)	
Mesial		125 (16.4)	633 (83.6)	
Lateral		17 (10.8)	141(89.2)	
Frontal		5 (5.3)	90 (94.7)	
Occipital		3 (15.8)	16 (84.2)	
Central/Parietal		2 (1.4)	142 (98.6)	
Temporal lobe	Awake	69 (9.7)	643 (90.3)	0.00
	Sleep	73 (35.8)	131 (64.2)	
Frontal lobe	Awake	2 (3.3)	59 (96.7)	0.246
	Sleep	3 (8.8)	31 (91.2)	
Central /parietal	Awake	2	106	0.411
	Sleep	-	36	
Non-localising	Awake	7	43	0.048
	Sleep	2	56	

All values are expressed as frequency (%). No seizures occurred during REM sleep. NS: not significant.

In our study, temporal lobe seizures occurred significantly more frequently during wakefulness, compared to other extratemporal locations, including frontal, occipital and central/parietal regions. The predilection of frontal lobe seizures occurring during sleep and temporal lobe seizures occurring during wakefulness has been documented in the literature and suggests that differential neuronal excitability of frontal and temporal lobe structures is involved in the activating mechanisms of sleep [6, 8, 16]. In a series by Crespel *et al*., of patients with refractory epilepsy who were candidates for epilepsy surgery (15 with frontal lobe epilepsy [FLE] and 15 with TLE), 61.1% of seizures in FLE occurred in sleep compared to 10.9% in TLE (p=0.01) [6]. Herman *et al*. reported 57.1% of frontal lobe seizures in their study in patients with focal drug-refractory epilepsy occurring during sleep, significantly more common during sleep than temporal or occipital lobe seizures [8]. In another study by Sinha *et al*., among patients with refractory epilepsy, 45.5% of frontal lobe seizures occurred during sleep [16]. The proportion of frontal lobe seizures arising in sleep was much lower in our study compared to the variable percentage observed in these studies, despite similar observations. This may be due to the relatively fewer patients with frontal lobe seizures overall included in our study. In addition, this might also be related to the sub-lobar localization within the frontal lobe and differential distribution of sleep-related hypermotor seizures (which occur exclusively during sleep) versus focal clonic and other seizure types.

In our study, lateral temporal lobe seizures were significantly more frequent during wakefulness compared to mesial temporal lobe seizures. Similar findings were reported by Herman *et al*. in their study, in which 75.9% of neocortical TLE seizures occurred during wakefulness compared to mesial temporal seizures (60%; p<0.0001) [8]. However, Crespel *et al*. found a higher proportion of mesial temporal seizures in the awake state, compared to mesial/mesio-lateral TLE combined, although this difference was not statistically significant [17]. Similar to this study by Crespel *et al*., in the subgroup of seizure-free operated patients in our study, seizures were more common during wakefulness although this subgroup included only mesial temporal epilepsy patients. Our findings suggest that sleep activates neocortical and mesial cortical structures in distinct manners. In another study by Goncharova *et al*., the spatial distribution of interictal spikes, as determined by intracranial EEG, varied with sleep and wakefulness in mesial and lateral TLE [18]. The proximity of mesial temporal regions to deeper structures involved in sleep control could potentially explain this observation. Hyper-synchronisation during sleep may have a higher likelihood, therefore, of triggering seizure activity from a mesial temporal focus. However, this is an intriguing association that needs further elucidation. The influence on sleep architecture by epilepsy, including TLE, has been investigated [19, 20]. Wakefulness after sleep onset (WASO) time has been reported to be longer in patients with refractory TLE compared to refractory FLE [6].

Our study has shown an overall higher frequency of secondary generalization of seizures during sleep, compared to wakefulness, similar to previous reports [8, 16, 21]. However, there was no statistical difference in the rates of secondary generalisation during different NREM stages. Seizure propagation during sleep, including NREM, is facilitated by a combination of neural generators of synchronised oscillations during slow-wave sleep and phasic sleep arousals in the form of sleep spindles and K complexes [1, 22]. On analysing individual lobes for secondary generalization, we found a higher frequency of secondary generalisation in temporal lobe, compared to extra-temporal seizures. Previously, Bazil *et al*. reported that 26% temporal lobe seizures and 21% frontal lobe seizures became secondary generalized, but the difference was not statistically significant [21]. Similarly, in the study by Herman *et al*., 17.5% of frontal, 22 % of temporal, and 35% of occipitoparietal seizures progressed to secondary generalization, which was also not statistically significant [8]. We would like to emphasize that, irrespective of the high predilection of frontal seizures occurring during sleep, the frequency of secondary generalisation during sleep was greater for temporal lobe seizures, in contrast to our overall subgroup. In the operated subgroup, the proportion of secondary generalisation was higher for frontal than temporal onset, in keeping with previous reports. These findings remain somewhat in line with interesting observations reported by Lambert *et al*., based on their stereo-EEG study on interictal spikes [23]. The authors found a significantly higher increase of interictal spikes in mesial temporal lobe regions during NREM sleep, compared to all other regions, suggesting high mesial temporal region propensity for spike production and propagation. The authors attributed this to specific local effects of sleep, *e.g*. more high-frequency oscillations and less slow waves in the mesial temporal regions during NREM sleep. In addition, one should take into account that recording of seizures in EMUs represents an unnatural scenario. Since the frequency of seizures among patients with TLE is typically lower compared to that for extra-TLE, the frequency of antiseizure medication reduction and withdrawal is likely to be higher among the former. This might also contribute to the more frequent secondary generalisation recorded in temporal lobe seizures in the overall subgroup.

We also examined the relationship between occurrence of seizures during wakefulness/sleep based on the underlying aetiology of focal epilepsy but could not find any clear association. Aetiology-based analysis of sleep/awake predilection has not been reported previously.

The main strength of this study is the evaluation of sleep/awake predilection for a large number of seizures among patients with drug-refractory epilepsy. This study adds important information to previous observations, based on this large set of data. We also studied the influence of sleep/awake state on seizures arising from mesial versus lateral/neocortical temporal locations as well as from other lobes. We additionally analysed the seizure-free subgroup who received surgery, which offered the opportunity to study these relationships with precise localisation.

Certainly, our study has some limitations. The study population was based on an adult epilepsy program, resulting in considerable heterogeneity as far as number of patients with temporal versus extratemporal-onset epilepsy was concerned. However, this represents the distribution in most adult epilepsy surgery programs, hence, it yields important information from a clinical practice standpoint. We recorded sleep states without using the standard additional electrodes used for polysomnography. Nonetheless, no difficulty was encountered in accurate sleep stage scoring. Further sleep parameter evaluation was, in any case, beyond the objectives of this study. Secondly, since this was a retrospective study, we could not collect information regarding seizure freedom after surgical resection in all our patients, although accuracy of localization was established in nearly a half of the included population (patients who had already undergone successful epilepsy surgery). Many of our patients had undergone anti-seizure medication tapering, depending on seizure frequency, epilepsy type and the presumed onset zone. We did not assess the effect of changes in antiseizure medication on seizure frequency and distribution during the sleep–awake cycle. Additionally, patients in the EMU are often sleep-deprived and undergoing antiseizure medication withdrawal which may influence sleep patterns, seizure frequency and the degree of seizure propagation to some extent. However, our study focussed on patients with refractory epilepsy who qualified for epilepsy surgery, a population for whom EMU admission is imperative. As such, the results from this study are clearly applicable to this population of patients with epilepsy. Moreover, we found very few patients with seizures arising from the parietal lobe which is a known issue with non-invasive localisation [21].

Conclusions

Our study demonstrates an association between lobar location of epileptogenic foci and a predilection of seizures occurring during sleep/awake state, with a tendency of seizures to become secondary generalized in drug-refractory epilepsy. Seizures with lateral temporal lobe as well as extratemporal lobe onset were more likely to occur during wakefulness. Overall, sleep related seizures were more likely to be of extratemporal lobe onset, though. ■

Supplementary material.

Supplementary tables accompanying the manuscript are available at www.epilepticdisorders.com.

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The authors have no conflicts of interest to report.

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TEST YOURSELF

(1) Which of the following statements holds true in terms of facilitation of focal seizures during sleep:
A. NREM sleep decreases the propensity for occurrence of seizures: (i) True (ii) False
B. REM stage of sleep increases the propensity for seizures: (i) True (ii) False

(2) Seizures during the awake state are more likely to arise from which of the following locations:
A. Lateral temporal lobe
B. Frontal lobe
C. Parietal lobe
D. Occipital lobe

(3) Secondary generalisation of focal seizures is more likely to occur during sleep in which of the following locations:
A. Lateral temporal lobe
B. Frontal lobe
C. Parietal lobe
D. Occipital lobe

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.