Large-scale network architecture and associated structural cortico-subcortical abnormalities in patients with sleep/awake-related seizures

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Abstract

Study Objectives: In this study, we aimed to estimate the alterations of brain networks and structural integrity linked to seizure occurrence during sleep and awake states.

Methods: Using a graph theory approach to magnetic resonance imaging-derived volumes of cortical and subcortical regions, we investigated the topological organization of structural networks in patients with sleep seizures (n = 13), patients with awake seizures (n = 12), and age- and sex-matched healthy controls (n = 10). Abnormalities in regional structural substrates (cortical volume/surface area, subcortical volumes) associated with sleep seizures and awake seizures were further analyzed.

Results: Brain networks in patients with sleep seizures compared to patients with awake seizures displayed a more integrated structural organization coupled with greater networks' stability. When compared to healthy controls, networks in both patients with sleep and awake seizures were analogously compromised, exhibiting a less integrated and preserved organization. Patients with sleep seizures in contrast to awake seizures had larger volumes of bilateral insula, superior temporal, and orbitofrontal cortices but lower volumes of left postcentral and right middle temporal cortices in comparison to healthy controls. Patients with awake seizures compared to healthy controls displayed reduced volumes mainly in frontal, temporal, and parietal regions of right hemisphere. Volumes of hippocampus, amygdala, caudate, pallidum, and putamen were larger in patients with sleep seizures than in patients with awake seizures.

Conclusions: Despite epileptogenesis, patients with sleep and awake seizures had distinct network and structural correlates across different epilepsy types. Identified regional cortical/subcortical abnormalities can endorse the pathophysiological alterations that induce seizures during the sleep or awake states.

Statement of Significance

Patients with sleep seizures and patients with awake seizures exhibited distinct topological organization of brain networks. Structural alterations differentiating between patients with sleep seizures and awake seizures involved cortical and subcortical regions. Identified network and structural abnormalities could be potentially linked to seizure occurrence during the sleep and awake states.

Key words: sleep seizures; awake seizures; network topology; structural correlates

Introduction

The occurrence of epileptic seizures throughout the day is a non-random phenomenon, strongly related to neural synchronization capturing locally and remotely interconnected cortical and/or subcortical networks [1–4]. The pathologically synchronized activity within epileptogenic networks is differentially modulated by particular alternating states of sleep and awake. Identification of structural correlates underlying the propensity of seizures to occur during the sleep or awake state might offer valuable details about the organization of the whole structural network. Extensive research pointed out the thalamo-cortical network as one putative partaker in the sleep/awake-related epileptogenesis in focal and generalized seizures [5–7]. Evidence implicating other brain regions that could be potential parts of the epileptogenic network is scarce.

At the same time, it is important to characterize not only the involved neuroanatomical substrates but also the topological characteristics of the networks' organization. Brain network properties as well exhibit dynamical sleep/awake-related reorganization [8] that could be addressed in order to better understand the impact of these states on seizure occurrence. But how the topological properties of the networks assign a higher pathological synchronizability to sleep or awake states is poorly understood. Given a frequency of 10%–15% of sleep seizures and a high risk of sudden unexpected death in epilepsy in these patients [9], based on emerging study results, more accurate sleep/awake-related seizure prediction models could be designed and a more diligent clinical guidance of patients with sleep seizures could be achieved.

Sleep and awake seizures are important pathophysiological models that can enhance our knowledge on epileptogenic networks. In this study, we assessed the large-scale network architecture (by constructing a common cortico-subcortical connectivity matrix) and the brain structural correlates of seizures occurring during the sleep and awake states. To do so, we analyzed (1) the magnetic resonance imaging (MRI)-derived topological network organization and (2) the evolving properties of cortical and subcortical structures in patients with sleep and awake seizures. We hypothesized that patients with sleep and awake seizures have distinct network topology alterations and structural abnormalities of cortico-subcortical anatomical substrates.

Methods

Study subjects

Over 5 years, from local video-electroencephalography (video-EEG) registry including 1,425 epilepsy patients, we identified 353 patients with seizures occurring either during the sleep or during the awake state. From these 353, patients (1) with advanced psychiatric comorbidities, (2) who underwent brain surgery for the cause of their epilepsy, (3) patients under age of 18 (children), (4) with acute symptomatic seizures (sleep deprivation, withdrawal seizures etc.), (5) lacking an MRI scan, and (6) who underwent an MRI scanning with different acquisition parameters were excluded. Afterwards, the patients identified with seizures occurring only during the sleep state were demographically (age, gender) and clinically (disease duration, seizure type, seizure frequency) matched with a group of patients presenting seizures only during the awake state. The group with sleep seizures included 13 patients (mean [*M*] age ± *SD* 28.7 ± 9.7 years, male-to-female ratio 9:4); the group with awake seizures consisted of 12 patients (26.3 ± 6.7 years, 3:9). All patients underwent comprehensive clinical, video-EEG and structural MRI work-up. The epilepsy type of the patients was established according to the updated International League Against Epilepsy (ILAE) classification of epilepsy [10]. Patient characteristics are highlighted in Table 1. A control group was included by recruiting 10 healthy subjects (28.3 ± 4.9 years, 6:4) without any history of seizures or psychiatric disorders and with normal MRI scans. All the subjects provided informed consent for the participation; the study was approved by the local ethical committee.

Video-EEG acquisition

Scalp EEG data, with simultaneous electrooculography (EOG) and electrocardiography (ECG), were recorded from 21 scalp positions; electrodes were placed according to the 10–20 international system. Patients with sleep seizures and awake seizures underwent a standard video-EEG recording, including intermittent photic stimulation and hyperventilation, followed by a continuous video-EEG monitoring during the daytime wakefulness and nighttime sleep with an overall duration of 48–72 hours. Sleep and awake states of the patients were determined by EEG and EOG. Video-EEG recordings with manifestations of seizures were interpreted by two experienced epileptologists (VC and DC). The identification of seizure type was based on the revised ILAE classification of seizures [11] and described according to the ILAE seizure semiology glossary [12].

MRI acquisition

Patients and healthy controls underwent 3T MRI using a 32-channel head coil Siemens Skyra scanner (Siemens Medical Solutions, Erlangen, Germany) with the following imaging sequences and parameters: T1-weighted images (repetition time [TR]: 1,900 milliseconds, echo time [TE]: 2.5 milliseconds, inversion time [TI]: 900 milliseconds, slice thickness [ST]: 1 mm, flip angle [FA]: 9°, field of view [FOV]: 100 × 100 mm^2, acquisition matrix: 256 × 256); T2-weighted images (TR: 6,860 milliseconds, TE: 58 milliseconds, ST: 2.5 mm, FA: 149°, FOV: 100 × 100 mm^2, acquisition matrix: 384 × 384); and 3D fluid-attenuated inversion recovery (FLAIR) images (TR: 5,000 milliseconds, TE: 388 milliseconds, TI: 1,800 milliseconds, ST: 0.9 mm, FA: 120°, FOV: 100 × 100 mm^2, acquisition matrix: 256 × 256].

MRI processing

T1-weighted images were processed with the FreeSurfer analysis software package (version 5.3.0, http://surfer.nmr.mgh.harvard.edu/); cortical surface reconstruction was performed in a fully automated fashion, followed by visual inspection for quality control at various processing steps [13, 14]. Briefly, for each subject, the surface-based processing stream consisted of skull stripping, Talairach space transformation, optimization of gray matter–white matter and gray matter–cerebrospinal fluid boundaries, segmentation of subcortical white matter, and deep gray matter structures and surface tessellation [15]. The cerebral cortex was then divided into 68 anatomical regions

Table 1. Demographical and clinical data of the patients

No	Gender	Age (years)	Epilepsy duration (years)	Epilepsy type	Seizure type	Seizure frequency	MRI	AEDs (mg/day)
Patients with sleep seizures								
1	M	34	30	Focal	Focal motor to bilateral tonic-clonic	1/week	Unremarkable	CBZ (900)
2	M	18	18	Generalized	Generalized myoclonic	1/week	Unremarkable	VPA (1,000)
3	M	17	2	Focal	Focal impaired awareness	1/year	Right HS	CBZ (900)
4	F	25	23	Focal	Focal hyperkinetic	1/week	Unremarkable	CBZ (675) + CLB (40)
5	M	18	8	Generalized	Generalized tonic	1/year	Unremarkable	CBZ (750)
6	M	50	2	Focal	Focal motor	1/half-yearly	Left temporal SC	CBZ (1,050)
7	F	38	26	Focal	Focal motor	1/month	Left frontal GMH	CBZ (1,050)+ LEV (2,000)
8	F	26	7	Generalized	Generalized tonic-clonic	1/month	Unremarkable	VPA (1,000)
9	M	32	19	Focal	Focal hyperkinetic	1/year	Unremarkable	CBZ (1,200)
10	M	29	18	Focal	Focal motor	1/half-yearly	Bilateral subcortical gliosis	CBZ (975)
11	M	19	3	Focal	Focal hyperkinetic	1/half-yearly	Unremarkable	CBZ (1,050)
12	M	38	13	Focal	Focal sensory	1/half-yearly	Left temporal encephalomalacia	LTG (250)
13	F	29	18	Focal	Focal impaired awareness	1/month	Unremarkable	CBZ (750)
Patients with awake seizures								
1	F	28	1	Focal	Focal motor	1/year	Left frontal glioma	CBZ (750)
2	F	50	22	Focal	Focal motor	1/month	Unremarkable	VPA (1,000) + LTG (750)
3	F	18	8	Generalized	Generalized tonic-clonic	1/half-yearly	Unremarkable	VPA (900)
4	F	18	1	Focal	Focal impaired awareness	1/week	Unremarkable	CBZ (1,350)
5	M	21	1	Focal	Focal sensory to bilateral tonic-clonic	1/year	Right fronto-parietal VM	CBZ (975)
6	F	18	15	Generalized	Generalized atonic	1/month	Unremarkable	VPA (1,000)
7	F	36	21	Focal	Focal autonomic	1/year	Right temporo-basal SC	LTG (150)
8	M	32	17	Focal	Focal autonomic	1/month	Bilateral HS	CBZ (1,200)
9	F	32	25	Focal	Focal autonomic	1/week	Right temporal SC	CBZ (900) + LTG (200)
10	F	19	1	Focal	Focal impaired awareness	1/half-yearly	Unremarkable	VPA (1,200)
11	F	30	20	Focal	Focal impaired awareness	1/month	Left HS	CBZ (900) + LTG (200)
12	M	16	1	Generalized	Generalized tonic-clonic	1/month	Unremarkable	CBZ (750)

CBZ, carbamazepine; CLB, clobazam; GMH, gray matter heterotopia; HS, hippocampal sclerosis; LTG, lamotrigine; SC, subarachnoid cyst; VM, vascular malformation; VPA, valproate.

according to the Desikan-Killiany atlas [16]. Regional cortical surface areas and cortical volumes were extracted. The volumes of seven subcortical structures directly or indirectly linked to epileptogenesis, namely the thalamus, hippocampus, amygdala, caudate, putamen, pallidum, and ventral diencephalon, were included in the subsequent analyses.

Staged analysis workflow is outlined in Figure 1.

Cortico-subcortical gray matter network construction

The extracted cortical and subcortical volumes from each region of interest (ROI) were embedded into a common structural connectivity (correlation) matrix (size 82 × 82) for each group. Each element from the connectivity matrix represents the Pearson correlation between the pairs of ROIs for each group. The generated connectivity matrices were used

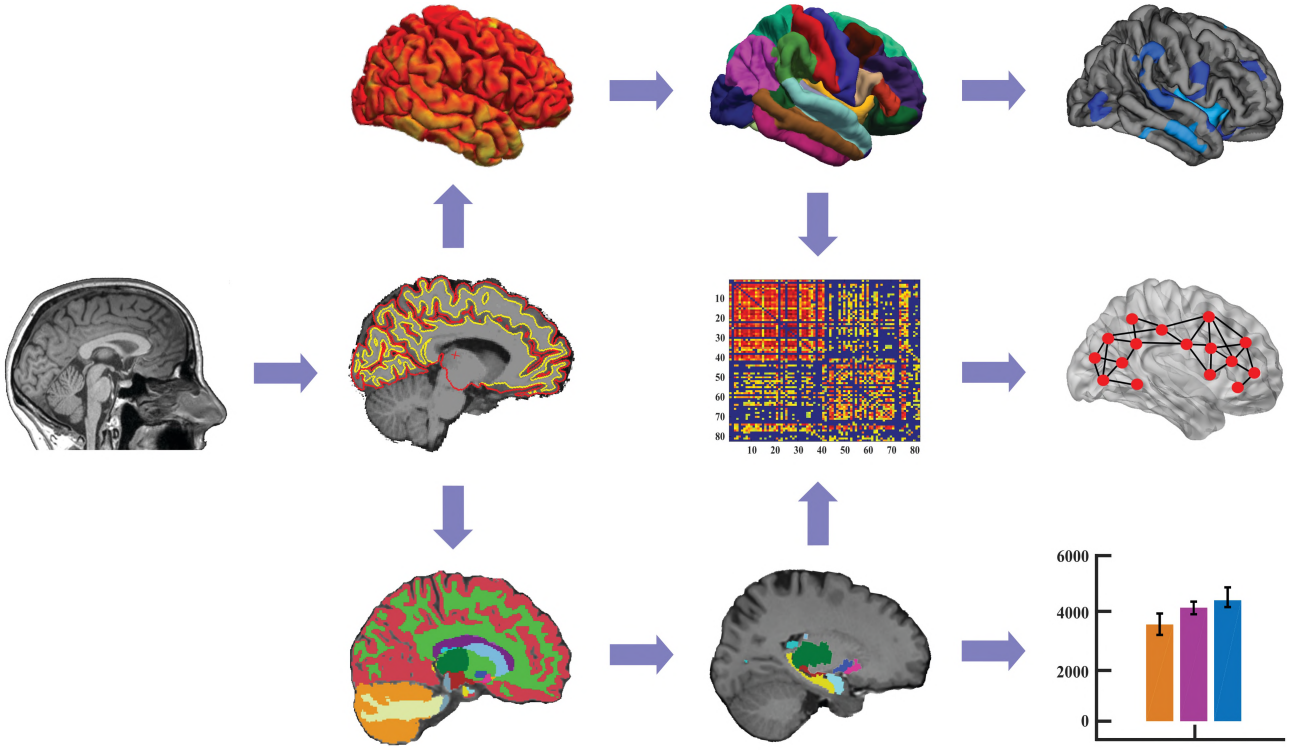

Figure 1. Data analysis pipeline. 3D T1-weighted images were segmented with FreeSurfer processing stream into cortical and subcortical regions of interest (ROIs). Extracted cortical and subcortical volumes from each ROI were used to construct group connectivity matrices and perform subsequent network analysis. Independently, between-group differences in volumes of cortical and subcortical ROIs were estimated.

for the subsequent network analysis using the graph-analysis toolbox (GAT) [17].

Structural network analysis

Network metrics were defined and calculated as previously established [18, 19]: *Characteristic path length* denotes the minimal number of edges that must be passed to go from one region to another; this measure is inversely related to the level of the network's integration. *Global efficiency* is the average of the inverse distance matrix of the whole network and is the parameter of integration, characterizing the efficiency of neural communication within the network. *Assortativity* is the preference of the network's node to connect to other similar nodes; assortative networks are more robust against computationally simulated removal of nodes. *Degree distribution* of a network denotes the probability distribution of the degrees (number of connections) over the entire network. Assortativity and degree distribution are measures of the network's resilience.

Statistical analysis

The statistical analysis was performed using SPSS software (version 23.0; IBM, Armonk, NY) and MATLAB R2015b (MathWorks, Natick, MA). Continuous variables are reported as $M \pm SD$; categorical variables are reported as absolute numbers (percentage). Group differences in demographic (age, gender), clinical (disease duration, seizure frequency, seizure type – focal vs generalized), and network variables were assessed with one-way analysis of variance (ANOVA), Mann–Whitney U or Pearson's χ^2, where appropriate.

After smoothing the surface data with a 10-mm Gaussian kernel, the built-in QDEC interface was used to address vertex-wise between-group differences in cortical surface area and volume between the groups via the general linear model. Statistical maps of significant differences were corrected for multiple comparisons using Monte Carlo permutation cluster analysis at a threshold of $p < 0.05$ ($Z = 1.3$).

A between-group comparison of subcortical volumes of patients and healthy controls was based on an ANOVA test with a 3 × 2 × 7 factorial design (group [3] × hemisphere [2] × subcortical volume [7]), followed by separate ANOVAs for each subcortical volume and Bonferroni post-hoc correction. The values of $p < 0.05$ were considered statistically significant.

Results

Subject characteristics

Study subjects from all three groups displayed no difference in terms of age ($F_{2,32} = 0.26$, $p = 0.77$) and gender (Pearson $\chi^2 = 5.103$, $df = 2$, $p = 0.08$). When comparing patients with sleep and awake seizures, the χ^2 test for seizure heterogeneity (focal vs generalized, $\chi^2 = 0.013$, $df = 1$, $p = 0.91$), Mann–Whitney U test for epilepsy duration ($U = 57.5$, $p = 0.26$), and seizure frequency ($U = 72.5$, $p = 0.76$) were not significant. In patients with sleep seizures, 10 (73%) had focal seizures and 3 (23%) had generalized seizures. In the group with awake seizures, nine (75%) patients presented focal seizures and three (25%) patients generalized seizures (see Table 1).

Network differences in sleep and awake seizures

The one-way ANOVA revealed higher path length not only in patients with awake seizures compared to those with sleep seizures ($F_{2, 57}$ = 69.605, p < 0.0001), but also in either patient group compared to healthy controls (p < 0.0001), indicating that the networks are less integrated on a global level in both patient groups (Figure 2). The impaired efficiency of neural communication within the networks was reflected by a lower global efficiency in patients with sleep and awake seizures in comparison to healthy controls ($F_{2,57}$ = 103.955, p < 0.0001). Patients with awake seizures showed higher assortativity than patients with sleep seizures ($F_{2, 57}$ = 57.220, p < 0.0001) or healthy controls (p < 0.0001), implying a higher tendency of nodes with similar properties to interconnect and higher resilience properties in patients with awake seizures. Additionally, we tested whether the degree distribution in the reconstructed networks followed an exponentially truncated power-law distribution. Here, the exponent estimate of the networks was 1.24 in patients with sleep seizures, 1.15 in patients with awake seizures, and 1.14 in healthy controls. The cutoff degree of the networks was 2.73 in sleep seizure patients, 2.97 in awake seizure patients, and 3.37 in healthy controls. The R^2 value of distribution fits was 0.95, 0.93, and 0.87 in patients with sleep seizures, awake seizures, and healthy controls, respectively.

Regional cortical differences in patients with sleep and awake seizures

The results of between-group differences are depicted in Figure 3. Clusters of significantly increased surface area in patients with sleep seizures in comparison to patients with awake seizures were identified mainly in insula and lateral orbitofrontal cortex of both hemispheres (Figure 3, A). Patients with sleep seizures also showed larger volumes of bilateral insula, superior temporal, and orbitofrontal cortices (Figure 3, A).

The left postcentral, right caudal middle frontal, and middle temporal cortices showed significantly reduced surface area in patients with sleep seizures in comparison to healthy controls (Figure 3, B). Also, the volumes of left postcentral and right middle temporal cortices were smaller in patients with sleep seizures (Figure 3, B).

Patients with awake seizures in comparison to healthy controls showed significantly decreased cortical surface area of left inferior parietal cortex and several regions of frontal, temporal, and occipital lobes from the right hemisphere (Figure 3, C). Patients with awake seizures also displayed reduced cortical volumes mainly in frontal, temporal, and parietal lobes of the right hemisphere (Figure 3, C). Detailed characteristics of the clusters are given in Supplementary Table S1.

Subcortical differences in patients with sleep and awake seizures

Hippocampus analysis showed a significant group difference ($F_{2, 32}$ = 3.643, p = 0.038) with post-hoc testing indicating larger volumes in patients with sleep vs awake seizures (p = 0.029). For amygdala, the analysis showed a similar group difference ($F_{2, 32}$ = 4.341, p = 0.021), with larger volumes in patients with sleep vs awake seizures (p = 0.030). The volumes of caudate and pallidum in patients with awake seizures were smaller than in patients with sleep seizures (p = 0.002 and p = 0.022, respectively) and healthy controls (p = 0.008 and p = 0.001, respectively). For putamen volume, post-hoc testing indicated significantly larger volumes in patients with sleep vs awake seizures (p = 0.001). Other subcortical structures (thalamus and ventral diencephalon) did not show any group difference. The results of ANOVA are represented in Table 2 and Figure 4.

Discussion

In this study, we addressed the MRI-derived large-scale network organization and the abnormalities of cortical and subcortical regions that provide the neuroanatomical substrate of sleep and wake seizures. We included patients with different seizure types (focal and generalized) in order to identify common structural alterations associated with distinct sleep/wake-related patterns of seizure occurrence across different epilepsy types. The topological architecture of brain networks in patients with sleep seizures displayed a better integrated network organization than in patients with awake seizures but with otherwise similar efficiency of neural communication. The networks in patients with either awake or sleep seizures both showed a higher assortativity than in healthy controls, and hence a higher adaptive capacity to counteract the detrimental effects of recurrent seizures. Despite epileptogenesis, patients with sleep and awake

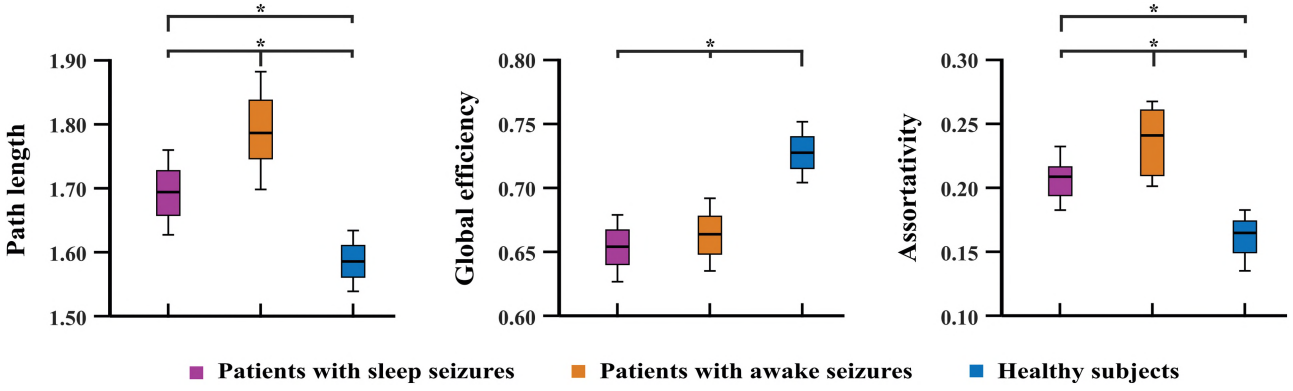

Figure 2. Box plots representing the differences in network measures (characteristic path length, global efficiency, and assortativity) between the patients with sleep seizures, patients with awake seizures, and healthy controls; *p < 0.001.

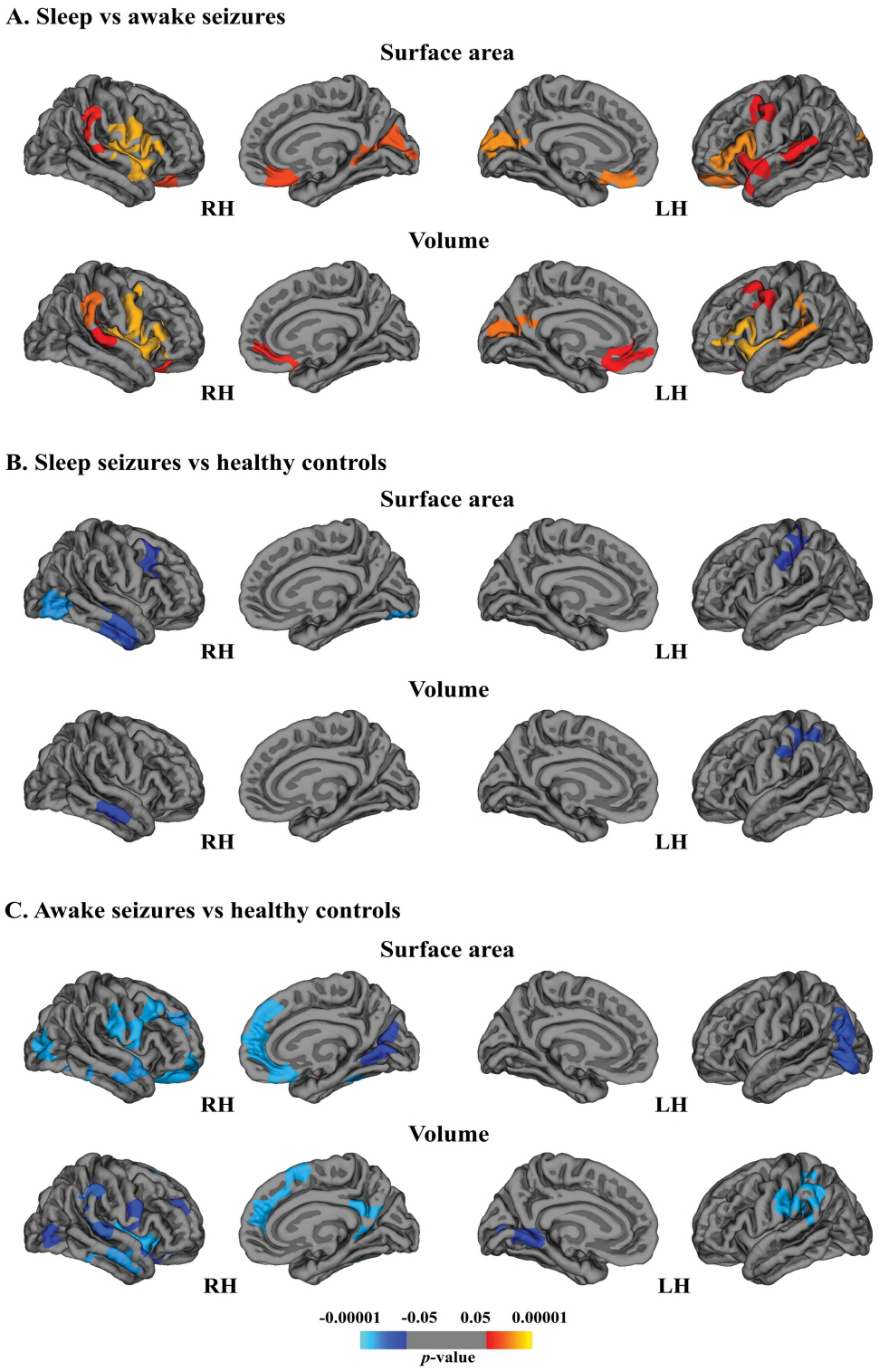

Figure 3. Statistical maps showing significant differences in cortical surface area and volume between (A) patients with sleep seizures and patients with awake seizures, (B) patients with sleep seizures and healthy controls, and (C) patients with awake seizures and healthy controls. Labeled clusters from the right (RH) and left (LH) hemispheres were significant after correction for multiple comparisons using Monte Carlo permutation at a threshold of $p < 0.05$ ($Z = 1.3$). The color bar represents statistical significance.

seizures exhibited distinct structural alterations involving mainly insular, frontal, and temporal cortices, and amygdala–hippocampal structures, with patients with sleep seizures displaying larger volumes within these regions.

Network correlates of sleep/wake seizures

Patients with sleep seizures in comparison to those with awake seizures had shorter path lengths, hence, a better global integration of the network architecture; however, the efficiency

Table 2. Volumetry of subcortical gray matter structures

Subcortical structure (mm^3)	Group				
	Patients with sleep seizures ($M \pm SD$)	Patients with awake seizures ($M \pm SD$)	Healthy controls ($M \pm SD$)	F	p
Thalamus	8208.6 ± 1006.1	8019.8 ± 1406.4	9131.2 ± 1515.0	2.973	NS
Hippocampus	4421.9 ± 621.0	3859.1 ± 508.1	4056.7 ± 1243.7	3.643	0.038
Amygdala	1797.3 ± 323.2	1500.5 ± 246.2	1415.2 ± 414.2	4.341	0.021
Caudate	3587.5 ± 395.2	3197.8 ± 532.5	3919.7 ± 435.9	8.092	0.001
Putamen	5949.7 ± 407.4	4690.1 ± 1041.8	5825.2 ± 1144.9	8.183	0.001
Pallidum	1427.4 ± 160.9	1147.3 ± 213.8	1414.4 ± 266.8	6.312	0.005
Ventral diencephalon	3965.4 ± 411.5	3614.7 ± 628.4	3835.8 ± 364.7	2.482	NS

NS, not significant.

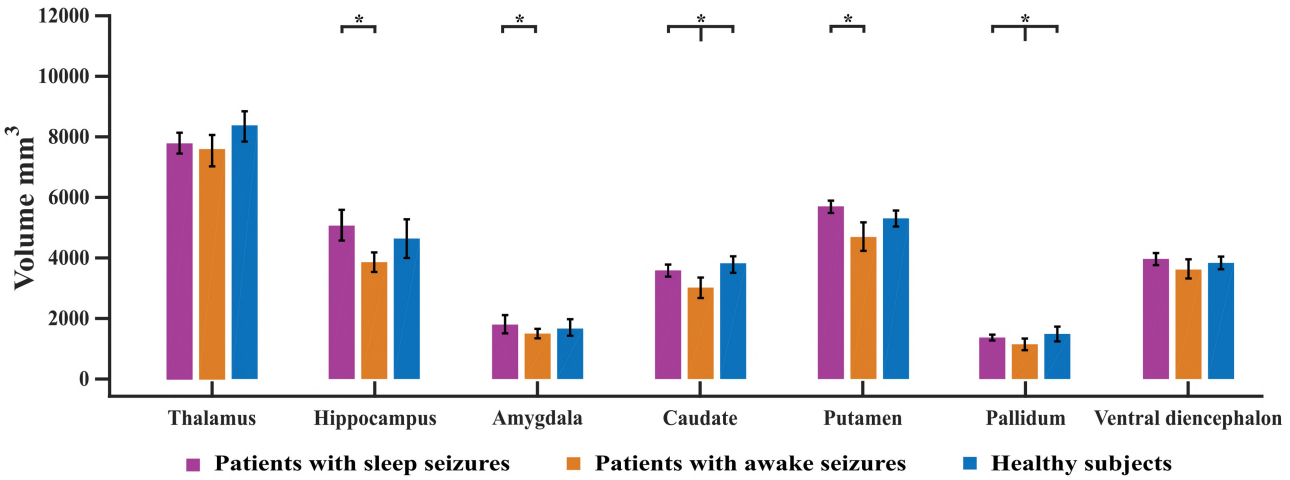

Figure 4. Bar plots representing the differences in volumes of subcortical structures between patients with sleep seizures, patients with awake seizures, and healthy controls; $^*p < 0.05$.

of neural communication within the networks (global efficiency) was similar in both groups but impaired when compared to healthy controls. In addition, the networks in patients with sleep seizures were less assortative than in patients with awake seizures. It is possible that during the awake state network nodes are tightly interconnected via hub-like structures, predisposing to increased assortativity, while during sleep the hub-like structures are less active, pushing the networks toward a state of decreased assortativity [20]. The fact that the degree distribution of all networks followed an exponentially truncated power law distribution suggests that in these networks, many regions have a small number of connections and only few regions have a large number of connections. Together with the increased network assortativity, the increased fit of the degree distribution of networks in patients with awake seizures and, to a lesser extent, in patients with sleep seizures, indicates that the involved networks have almost equal capacity to withstand the effects of repeated seizures [21], thus losing their plastic and flexible behavior. One can speculate that this network stability has considerable effects in mitigating the loss of network functionality in conditions of recurrent seizures. Indeed, the path lengths of these networks were increased, possibly reflecting an effort to reorganize and compensate the aberrant local seizure tendency to propagate and inducing the observed loss of topological flexibility.

Regional structural correlates of sleep/wake seizures

Up to now, most of the research in epileptogenesis [7, 22–24] has addressed only whether cortical and subcortical brain abnormalities depend on seizure-onset zone localization, hemisphere, or specific syndrome, but has not considered dependency of the evolving seizures on sleep or wake states. Comparing the structural integrity between the patients with sleep and awake seizures, we characterized widespread involvement of cortical and subcortical gray matter substrates, detecting a possible relation to sleep/awake propensity of seizure occurrence. In particular, the larger volumes of insular, orbitofrontal, and superior temporal cortices, together with volumes of hippocampus, amygdala, and basal ganglia, in patients with sleep seizures in comparison to patients with awake seizures might be attributed to the differences in mechanisms of epileptogenesis depending on the brain state.

Thalamic nuclei and thalamo-cortical networks producing oscillations during sleep modulate the synchronizability of the remote cortical regions [25]. Thalamo-cortical circuits that are involved in the generation of sleep spindles are as well engaged in the generation of spike-wave discharges in generalized seizures [26]. Sleep/awake activation of these circuits may influence the occurrence of sleep or awake seizures within certain epilepsy types [5]. Patients with sleep and awake seizures showed no difference in the thalamic integrity, perhaps

due to (1) the fact that alterations of thalamic volume were not captured by the whole analysis of the thalamus and thus the estimation of thalamic subregions is required or (2) the sample size of the patient groups which may not sufficiently depict the volumetric differences between the studied groups.

In addition to conventional MRI, diffusion tensor imaging (DTI) and tractography can provide useful details on structural properties and connectivity of white matter tracts composing the networks in sleep/awake-related seizures. Past and present evidence recognized the valuable role of DTI–fiber tractography in noninvasive characterization of microstructural milieu of epileptogenic networks [2, 27], mapping the cortico-subcortical neural circuitries [28] and tracking the reorganization of nerve fiber tracts [29]. On one hand, the white matter exhibits clear structural variations in relation to sleep/awake rhythmicity [30, 31] involving frontotemporal and parieto-occipital areas and thalamus [30]. On the other hand, individual dynamics of sleep oscillations depend on regional microstructural characteristics of white matter tracts in the temporal lobe, and within and neighboring the thalamus [32]. Notably, these data point out the relevance of subcortico-cortical microanatomy and connectivity not only in sleep/awake expression of neural synchronization but also possible implications for state-dependent seizure generation. However, the studies based on DTI–fiber tractography methods are prone to difficulties in tracking the brain areas with complex architecture of white matter fiber crossing. In these cases, an accurate and reliable delineation can be achieved by high angular resolution diffusion imaging (HARDI), especially when combined with compressed sensing techniques [33]. The HARDI algorithms showed promising results in depiction of structural network connectivity in epilepsy [34] and functional network underpinnings of sleep and awake states [35].

Clinical significance

Monitoring the fluctuations in seizure occurrence depending on the sleep/awake states might serve for the development of seizure prediction models [36]. Therefore, a precise characterization of the involved structural network is needed. Moreover, a better delineation of the epileptogenic zone during the presurgical evaluation could be achieved by the knowledge of specific sleep/awake-related seizure patterns. Adjustment of seizure prevention therapy to individual sleep/awake-related seizure patterns may improve the effects of antiepileptic drugs (AEDs) and achieve a greater control during the states of highest proneness to seizures. However, more comprehensive research is required to investigate the interaction between the sleep/awake seizure patterns, circadian/multidien oscillators, and exogenous daily rhythms in order to identify predictive markers for a more tailored management of epilepsy.

Limitations

Our study has several limitations. First, the sample size of the patient groups was relatively small and could have maximized the extent of differences in cortical and subcortical volumes. Second, for the analysis of network parameters, we used only structurally derived connectivity information without addressing functional data from EEG. The integration of different modalities might provide more precise information about seizure events and deal with modality-specific disadvantages. Patients with sleep and awake seizures presented various structural causes of their focal seizures that could in a differential manner impact the integrity of specific cortical and/or subcortical structures and associated network parameters. Patients' actual and even past long-term treatment with AEDs could also influence the above-mentioned structural and associated network parameters. At the same time, it is difficult to assign all the identified abnormalities only to the sleep/awake states, since common neuroanatomical alterations are inherent to a wide spectrum of epilepsy types [37]. Future studies enrolling larger number of patients with identical/similar epilepsy syndromes, integrating structural and functional data, will clarify the emerging challenges of this issue.

Conclusions

We showed that despite epileptogenesis, patients with sleep or awake seizures had distinct network and anatomical correlates in a transdiagnostic matter and across epilepsy types. These abnormalities capturing cortical and subcortical regions could be regarded as potential substrates promoting the seizure occurrence during the sleep or awake states. Mapping the networks' elements and topological organization that are relevant for the brain state-related patterns of seizure generation is a promising road toward personalized therapeutic approaches and biomarker discovery for seizure prediction.

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Conflict of interest statement. None declared.

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