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FULL-LENGTH ORIGINAL RESEARCH

From mesial temporal lobe to temporoperisylvian seizures: A quantified study of temporal lobe seizure networks

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Summary

Purpose: **The determination of epileptogenic structures in partial epilepsy is crucial in the context of epilepsy surgery. In this study we have quantified the "epileptogenicity" of mesial temporal lobe structures (M), lateral neocortical regions (L), and extratemporal perisylvian structures (ET) in patients with temporal lobe epilepsy (TLE), in order to classify the brain networks involved in seizure generation.**

Methods: **Thirty-four patients having TLE investigated by intracerebral recordings using stereotactic electroencephalography (EEG) (SEEG) were selected. Epileptogenicity of M, L, and ET structures was quantified according to the "epileptogenicity index" (EI), a new way to quantify rapid discharges at seizure onset, ranging from 0 (no epileptogenicity) to 1 (maximal epileptogenicity).**

Results: **Automatic clustering using EI values from M, L, and ET separated patients into four classes: mesial group (max EI in M), lateral group (max EI in L), mesiolateral group (high EI in both M and L) and temporoperisylvian group (TPS) (high values in ET). The median number of highly epileptogenic structures (defined by EI >0.3) was four, a result confirming that most TLE is organized as "epileptogenic networks." We found that the duration of epilepsy was correlated with the number of epileptogenic structures and that surgical prognosis was also related to the extent of the epileptogenicity in the brain.**

Conclusions: **Several distinct epileptogenic networks are involved in seizure generation in TLE. Findings advocate for a progressive recruitment of epileptogenic structures in human brain with time.**

KEY WORDS: **Rapid discharge, Temporal lobe epilepsy, SEEG, Prognosis, Epileptogenesis.**

Temporal lobe epilepsies (TLEs) are particularly frequent forms of drug-resistant partial epilepsies and may be remediable by surgery. It is classically recognized that TLE may disclose two main types of epileptogenic zone (EZ, the brain structures that generate seizures (Bancaud et al., 1970)), defining the mesial temporal lobe subtype (in which the EZ is localized in the temporal mesial lobe) or the lateral subtype (in which the EZ is localized into the neocortex) (Gil-Nagel & Risinger, 1997; Williamson et al., 1998). These two forms may be distinguished according to etiology or ictal electroclinical semiology.

However, this classification (Commission, 1989) has been challenged by studies using lateral/orthogonal depth electrodes (stereotactic electroencephalography, SEEG) showing that other forms of TLE seizures may be observed (Talairach et al., 1974; Bancaud, 1981; Rasmussen, 1982; Wieser, 1983; Munari et al., 1994; Bartolomei et al., 1999, 2001; Maillard et al., 2004; Barba et al., 2007). In particular, it has been shown that some TLEs are characterized by more complex EZ, including both mesial (M) and lateral (L) cortices (mesiolateral subtypes) (Bartolomei et al., 1999, 2001; Maillard et al., 2004). Temporal lobe seizures involving the cortices lining with the sylvian fissure (''perisylvian cortices'') have been described for a long time in the SEEG literature (Talairach et al., 1974; Munari et al., 1980; Isnard et al., 2004). Perisylvian cortices constitute a phylogenetic and physiologic system in the mammalian brains including the operculoinsular cortices and the ''limbic'' part of the orbitofrontal cortex (Mesulam & Mufson, 1982).

Recently, the existence of complex epileptogenic networks, including temporal lobe structures and adjacent extratemporal cortices, has led to the acronym ''temporal

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plus'' seizures (Ryvlin & Kahane, 2005; Barba et al., 2007). Temporal plus epilepsies include temporooccipital epilepsies and temporoperisylvian epilepsies. These seizures may be suspected from clinical features suggestive of extratemporal involvement (such as gustatory or auditory hallucinations) and more prominent EEG abnormalities. The extension of the EZ outside the limit of the surgical resection is thought to be a major cause of epilepsy surgery failure, particularly when focal or conservative surgery has been proposed in a given patient (Ryvlin & Kahane, 2005).

However to date, no previous study has used a precise quantification of the EZ for the definition of the epileptogenic networks initially involved in seizure generation. Therefore, the existence of several subtypes of TLE seizures is still subject to debate (Gil-Nagel & Risinger, 1997).

Herein we propose a more objective quantification of the EZ by the estimation of a mathematical quantity called ''epileptogenicity index'' in brain structures involved (or not) by the ictal discharge (Bartolomei et al., 2008a). This study is aimed at defining whether subgroups of TLE seizures may be defined according to the respective involvement of mesial (M), lateral (neocortical temporal, L) or extratemporal ''perisylvian'' cortices (ET) at seizure onset. In this study, seizures were recorded using depth-electrodes according to the SEEG technique. Secondary objectives include an investigation of the relationship between the type of epileptogenic network and the etiology and the surgical prognosis.

Methods

Patient selection and SEEG recording

Thirty-four consecutive patients undergoing presurgical evaluation of drug-resistant TLE were selected from a series of 100 patients in whom intracerebral recordings had been performed between 2001 and 2006.

All patients had a comprehensive evaluation including detailed history and neurologic examination, neuropsychological testing, routine magnetic resonance imaging (MRI), surface electroencephalography (EEG), and SEEG (depth electrodes).

SEEG exploration was carried out during long-term video-EEG monitoring. Recordings were performed using intracerebral multiple contact electrodes (10–15 contacts, length: 2 mm, diameter: 0.8, 1.5 mm apart) placed according to Talairach's stereotactic method (Bancaud et al., 1970; Talairach et al., 1992), as illustrated in Fig. 1.

The anatomic targeting of electrodes was established individually, according to available noninvasive information and hypotheses about the localization of the epileptogenic zone. A preplanning of the implantation was performed on three-dimensional (3D) T1 MRI images using dedicated software (''Brainvisa,'' http://brainvisa.info) for surface rendering calculation, cortical anatomy analysis, and sulcal labeling (Mangin et al., 2004; Regis et al., 2005). The final definition of each electrode trajectory was elaborated on a workstation allowing stereotactic registration of preoperative stereotactic MR and preoperative stereotactic telemetric angiography. A postoperative computerized tomography (CT) scan without contrast was then used to verify the absence of bleeding and the position of electrodes. Video-EEG recording was prolonged as long as necessary in order to record several of the patient's habitual seizures. Intracerebral electrodes were then removed and an MRI performed, permitting visualization of the trajectory of each electrode (3D T_1-weighted images and T_2-weighted coronal images; Siemens 1.5T [Siemens, Berlin, Germany]). Finally, computed tomography (CT) scan/MRI data fusion was performed to accurately check the anatomic location of each contact along the electrode trajectory according to previously described procedures (Bartolomei et al., 2004). All patients had electrodes that spatially sampled mesial/limbic regions (including amygdala, A; entorhinal cortex, EC; internal part of the temporal pole, iTp; the anterior part of the hippocampus, HiA; the posterior part of the hippocampus,HiP) and lateral/neocortical regions of temporal lobe (external part of the temporal pole, eTP; anterior part of the middle temporal gyrus, aMTG; posterior part of the middle temporal gyrus, pMTG; superior temporal gyrus, STG). All selected patients also had electrodes exploring at least one extratemporal perisylvian region (the orbitofrontal cortex, OFC; the operculoinsular region through the frontal operculum, OP; or the temporal operculum, INS) in order to determine the extension of the EZ to these regions or to study the propagation of seizures (see Fig. 1B).

Signals were recorded on a 128 channel Deltamed system (Deltamed, Paris, France). They were sampled at 256 or 512 Hz and recorded on a hard disk (16 bits/sample) using no digital filter. A high-pass filter (cutoff frequency equal to 0.16 Hz at −3 dB) was used to remove very slow variations that sometimes contaminate the baseline. A first-order low-pass filter (cut-off frequency equal to 97 Hz at −3 dB) was used to avoid aliasing. Table 1 provides clinical information about the patients selected for the purpose of this study.

SEEG signal analysis: computation of the epileptogenicity index (EI)

The EI is a measure aimed at quantifying the epileptogenicity of brain structures recorded with depth electrodes. This method was recently proposed in previous papers (Bartolomei et al., 2008a; Aubert et al., 2009; Vaugier et al., 2009) where an extensive description is provided. In this section, we provide a short summary about the main features of this index along with the main methodologic aspects. The EI is intended to quantify two important features of SEEG signals when recorded during the transition from preictal to ictal activity: (1) the redistribution of signal energy from lower frequency band (theta, alpha) toward higher frequency band (beta, gamma) and (2) the delay of appearance of these high-frequency components in a given

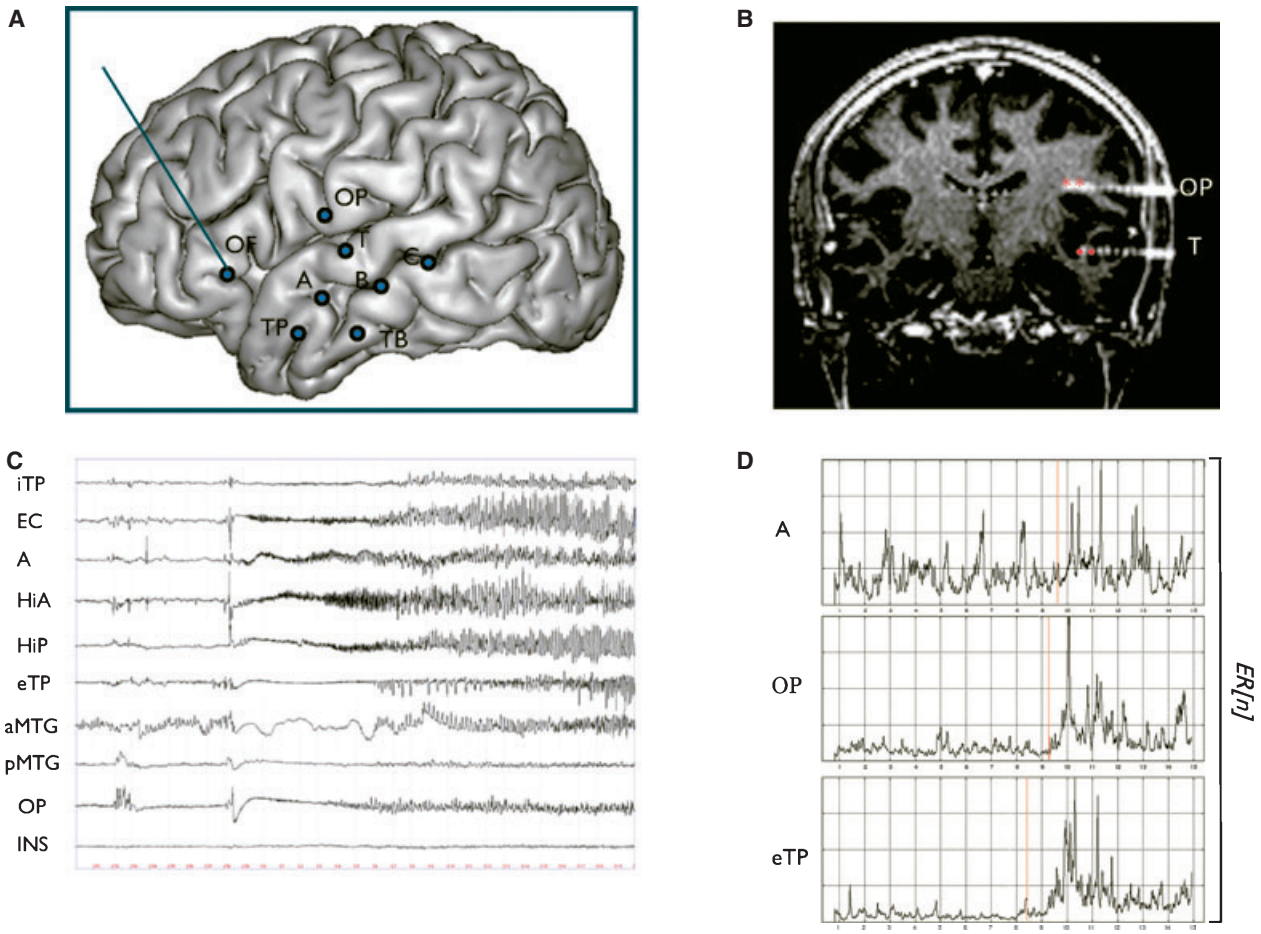

Figure 1.

Example of depth electrode implantation for stereoelectroencephalography (SEEG) exploration in temporal lobe epilepsy (patient P30) and signal analysis. (**A**) Lateral view of all depth electrodes superimposed on a 3D reconstruction of the neocortical surface of the brain. In this case, brain structures are explored with eight intracerebral multiple contact electrodes denoted by letters A, B, C, Tp, Tb, T, OF, and OP. Internal contacts of electrodes Tp, A, B, and C record four mesial structures (respectively, the internal part of the temporal pole, the amygdala, the anterior hippocampus, and the posterior hippocampus), whereas external contacts record four lateral structures (respectively, the external part of the temporal pole, the anterior, the middle, and the posterior part of MTG). Internal and external contacts of electrode T explore two main structures (respectively): the temporal part of the insula and the superior temporal gyrus). Internal contacts of electrode Tb reaches the entorhinal cortex. Electrode OF is an oblique electrode reaching the orbitofrontal cortex (OFC) and electrode OP records the frontal operculoinsular cortex (OP). (**B**) Reconstruction of the trajectory of the electrodes OP and T superimposed on the coronal MRI view. (**C**) SEEG recordings with selected traces from different structures during a seizure. iTP, internal part of the temporal pole; eTP, external part of the temporal pole; OFC, orbitofrontal cortex; A, amygdala; HIA, anterior hippocampus; HIP, posterior hippocampus; EC, entorhinal cortex; aMTG, anterior middle temporal gyrus; pMTG, posterior part middle temporal gyrus. (**D**) Increase in energy ratio ER[*n*] is shown in three SEEG signals from temporal pole (eTP), opercular cortex (OP), and amygdala (A). The Page-Hinckley algorithm provides a detection time N_{d_i} (orange marks) for each brain structure if involved in the generation of a rapid discharge. The first detection time is arbitrarily defined as the reference time N_0 (eTP in this case).

structure with respect to the first structure, itself involved on a ''rapid discharge mode.'' In this respect, the EI is built on the same information as the one that is searched for during visual review of EEG seizure recordings. Nevertheless, the EI allows the user to go beyond the qualitative description of data, as it provides a quantitative measure that increases with increase of high-frequency components and short delay of involvement. In addition, this quantitative measure can be used for classification. In practice, we use a semiautomatic approach: Using a handy graphical user interface, the user can easily inspect and validate automatically detected change points indicating the accurate onset of rapid

Table 1. Main clinical features of the 34 studied patients (P1-P34)

Patients	Epilepsy duration (y)	Age at onset (y)	MRI/ etiology	Side	Aura	LOC	Atypical objective signs	SGTCS	EI>0,3	Subtype	Surgical procedure	Surgical outcome	Follow up (y)
P1	32	3	Le	R	ES, Emo	No		No	5	M	ATL	I	4
P2	15	16	Le	R	Olf	Early		Rare	4	ML	ATL	I	5
P3	37	8	HS	Left	ES, Emo	Late		Rare	4	M	ATL	I	6
P4	35	17	N	R	No	Early	HK features	Rare	5	ML	NO	NO	_
P5	30	3	N	Left	ES, Emo, DV	Late		Rare	7	ML	ATL	III	4
P6	15	14	HS	R	Es, TA	Late		Rare	3	M	ATL	I	5
P7	14	20	Le	R	ES, TA	Early		Rare	10	TPS	NO	NO	_
P8	11	3	HS	Left	No	Late		Rare	2	M	ATL	I	6
P9	15	17	HS	Left	Olf, DV	Late		Frequent	2	M	ATL	II	6
P10	28	14	N	R	DV, VI	Early		Frequent	8	ML	ATL	III	3
P11	18	11	N	Left	No	Early		Frequent	5	ML	NO	NO	_
P12	11	7	N	R	Emo	Early	HK features	Rare	3	M	ATL+OFC	II	2
P13	51	1	N	R	No	Early	Bilateral tonic posture	Frequent	3	TPS	NO	NO	_
P14	35	7	N	R	Aud	Early		Frequent	6	L	CT	I	6
P15	20	10	HS	R	ES, DV	Late		No	3	M	ATL	I	7
P16	28	2	HS	R	Emo, TA	Late		No	3	M	ATL	II	7
P17	20	10	HS	Left	No	Early		Rare	3	M	ATL	I	6
P18	21	1	Le	R	DV	Early		Rare	4	ML	ATL	I	6
P19	37	6	HS	R	ES	Late	Delayed HK features	Rare	3	M	ATL	I	2
P20	20	3	Le	R	Aud	No		Frequent	1	L	CT	I	5
P21	12	5	HS	Left	No	Early		Rare	4	M	ATL	I	5
P22	47	9	HS	R	ES, Emo	Late	Delayed HK features	Rare	7	ML	ATL	I	2
P23	29	3	HS	R	ES, Emo, Gus	Late		Rare	4	M	ATL	I	5
P24	12	30	N	R	Aud, vertigo	Late		Frequent	1	L	CT	I	2
P25	20	16	HS	R	ES	No		Rare	3	M	ATL	I	6
P26	25	15	N	Left	ES, Emo, TA, Gus	No		Rare	2	M	ATL	I	6
P27	13	25	HS	Left	No	Late		Rare	2	M	ATL	I	7
P28	18	4	HS	R	ES, Emo	Late		Rare	5	M	AHGK	I	7
P29	18	18	N	Left	Emo	Early		Rare	6	ML	NO	NO	_
P30	35	28	N	Left	Aud, Emo, DV	Early	Hemifacial contraction, salivation	Frequent	7	TPS	ATL*	III	4
P31	11	12	N	R	No	Early	Early contralateral head deviation	Frequent	9	TPS	ATL*	III	2
P32	20	5	Le	R	Aud	No		Rare	1	L	CT	I	8
P33	2	14	Le	Left	Aud	No		Rare	1	L	NO	NO	_
P34	23	1	Le	Left	TA	Early		Frequent	6	ML	ATL°	III	5

Surgical outcome refers to the Engel classification (follow-up duration >2 years for all patients). (*) and (°) indicate that the resection was considered to be incomplete with regard to the results of SEEG analysis. (*) Resection did not include extratemporal cortices. (°) indicates that in this case the resection was not considered to be complete due to the posterior extension in the medial temporal lobe of the epileptogenic zone.

ATL, anterior temporal lobectomy; ATL+OFC, anterior temporal lobectomy associated with orbitofrontal resection; AHGK, amygdalohippocampectomy gamma knife; NO, not operated; SGTCS, secondary generalized tonic–clonic seizures (no, none; rare, <2/year; frequent, >2/year); LOC, loss of consciousness, (early, <10 s; late, >10 s after seizure onset); Aud, auditory hallucinations or illusions; Olf, olfactory hallucinations; Gus, gustatory hallucinations; Vi, complex visual hallucinations; DV, deja vu; Emo–, negative emotional feeling; Es, epigastric sensation; TA, thermoregulatory alteration (cold or hot sensation, shivering); HS, hippocampal sclerosis; N, normal MRI; $N_{EI \geq 0.3}$, number of brain structures disclosing an epileptogenicity index value >0.3; Le, lesion other than HS; R, right; Subtypes: M, mesial; ML, mesiolateral; TPS, temporoperisylvian; L, lateral.

discharges. From this validation performed on a ''structure-by-structure'' basis, the EI is then computed.

The EI is a normalized quantity (ranging from 0 to 1) that is computed from depth-EEG signals. This quantity may be estimated using a two-stage procedure. (1) First, over a sliding window, the signal energy ratio (*ER*) is computed, between high [β (12.4–24 Hz) and γ (24–90 Hz)] and low [θ (3.4–7.4 Hz) and α (7.4–12.4 Hz)] frequency bands of the EEG from the signal spectral density $\Gamma(w)$ (squared modulus of its Fourier transform). (2) Second, we detect change-points in the *ER[n]* quantity, which is sensitive to frequency changes in the signal. In particular, we use an optimal algorithm (''cumulative sum algorithm'' or ''CUSUM'') to automatically determine the time instant when ER[n] increases, that is, when θ–α activity (that is predominant in background SEEG signals) changes into β–γ

activity (that is predominant in SEEG signals during rapid discharges) (see examples in Fig. 1).

These two steps allow for the computation of the Epileptogenicity Index EI_i from the SEEG signal s_i recorded from brain structure S_i:

$$\mathrm{EI_i} = \frac{1}{N_{d_i} - N_0 + \tau} \sum_{n=N_{d_i}}^{N_{d_i}+H} \mathrm{ER}[n],\ \tau > 0$$

where N_0 is the time instant corresponding to seizure onset (defined hereafter) andN_{d_i} is the detection time in signal s_i recorded from structure S_i and H is the duration over which ER[n] is integrated. Parameter τ accounts for the particular, where S_i is the first structure that generates the fast activity ($N_{d_i} = N_0$, seizure onset) and avoids division by zero. It was arbitrarily set to 1. Parameter H was set to be equal to 5 s, as previously defined to detect the onset of rapid discharges (Bartolomei et al., 2008a). This method is applied over the whole duration of the seizure using a sliding window (5 s). On each channel, the first detected change-point corresponds to the onset of the rapid discharge (if present).

Finally, in order to obtain a normalized value ranging from 0 (no epileptogenicity) to 1 (maximal epileptogenicity) for considered structures S_i, EI_i values were divided by the maximal value obtained in each patient. In the sequel, normalized EI_i values are simply denoted by ''EI values.''

EIs were calculated from mesial temporal lobe structures (A, HiA, HiP, EC, iTP) as well as from some lateral cortices (eTP, aMTG, pMTG, STG) or in perisylvian extratemporal cortices [ET: frontal operculoinsular cortex (OP), orbitofrontal cortex (OFC), and/or insular temporal cortex (INS)]. The two first spontaneous seizures recorded during video-SEEG monitoring were studied.

During the transition between interictal period and ictal rapid discharges we may observe two main patterns, as defined in previous studies (Engel et al., 1989; Spencer et al., 1992; Bartolomei et al., 2005). The transition from interictal to ictal activity may be characterized by the emergence of a low-frequency high-amplitude rhythmic spiking followed by the rapid discharge, or in other cases the seizure onset is characterized by the emergence of the rapid discharge without prior spiking. In the present study, EI determination was based on the detection and quantification of rapid discharge, whatever the existence or not of a preictal spiking. Table S1 provides a list of the different explored structures along with corresponding EI values.

Clustering classification and statistical analysis

A first attempt to classify TLE networks was performed using an automatic classification. Maximal EI values obtained from either mesial structures (M), lateral cortices (L), or extratemporal cortices (ET) were determined for each patient (Table 1). Therefore, for each patient, three values (M, L, and ET) were determined. These three values were first used in an attempt to classify the networks using a k-means classification method. The k-means (MacQueen, 1967) is one of the simplest and most commonly used algorithms to partition a multidimensional dataset into k clusters. It is an iterative algorithm that aims to minimize the total within-cluster variance (i.e., the sum of the squares of the distances between each data point and its cluster center). A major drawback of the k-means algorithm is that the quality of the final partition strongly depends on the initial (typically, randomly selected) cluster centers. In practice, this effect can be reduced by running the algorithm multiple times with different sets of initial cluster centers and by returning the best partition found (i.e., the one with the minimum within-cluster inertia). In addition, in the k-means algorithm, the number k of clusters must be fixed a priori. Therefore, we complemented the algorithm by a procedure aimed at determining an optimal value for k. This procedure consists in running the k-means algorithm for an increasing number of clusters (from 2 to 10). For each partition, we computed the so-called R-square criterion (defined as the ratio of the intercluster inertia to the total inertia) as a function of the number k of clusters. The k-means results will be compared to our clinical assumption that there might exist four main subtypes of TLE seizures: mesial (M), lateral (L), mesiolateral (ML), and temporoperisylvian (TPS).

To determine if epileptogenicity profiles are different in the population of patients with M and ML subtypes, EI values obtained in mesial structures were compared using analysis of variance (ANOVA) with groups as an independent factor (M vs. ML) and EI values as dependent factors. Because the statistical distribution of the EI values was determined not to be gaussian, ANOVA was performed using log transformed data.

Post hoc tests using Bonferroni correction for multiple comparisons were then used for the comparison of each structure value. Chi-square was used to compare the distribution of the four subtypes according to the underlying etiology. A nonparametric Spearman correlation was used to find correlation between age at epilepsy onset, epilepsy duration, and the size of the epileptogenic zone as reflected by the number of structures disclosing IE >0.3. EI values between seizure-free (SF, Engel class I) patients and not seizure-free (not SF) patients were compared using the nonparametric Mann-Whitney test. A p-value <0.05 was considered to be significant.

Results

Table 1 summarizes the clinical characteristics of the 34 included patients.

Classification of TLE networks

EI values from different explored brain structures were computed (and averaged from two seizures) in each patient as indicated in Table S1. According to the inclusion criteria, most of the patients had maximal values in the temporal

lobe. It is noteworthy, however, that some patients disclosed high EI values in perisylvian cortex.

To classify the involved networks, for each patient, we took the maximal EI values obtained from mesial structures (A, EC, iTp, HA, HP), from the lateral temporal neocortex (eTp, aMTG, pMTG) and from extratemporal cortex (INS, OP, OFC). The *k*-means classification allowed us to determine that a clustering into four groups was ''optimal'' according to the *R*-square criterion (defined as the ratio of the intercluster inertia to the total inertia). Indeed, as depicted in the curve provided in Fig. 2B, it can be verified that (1) 90% of the total variance is obtained for four groups and (2) the gradient of the *R*-square quantity drops from 10–2% when the number of classes goes from 4–5. This result indicates that partitions that include $k = 5$ groups (or more) are not so different in terms of interclass and intraclass variance, when compared to the one obtained for $k = 4$ groups. Interestingly, this number corresponds to our clinical assumption according to which there exist four main subtypes of TLE seizures.

The first group included 16 patients with high values in mesial structures (1) and low values in L (range 0–0.18) or ET cortices (range 0.01–0.2). This group corresponded to pure mesial TLE seizures (M group). A second group

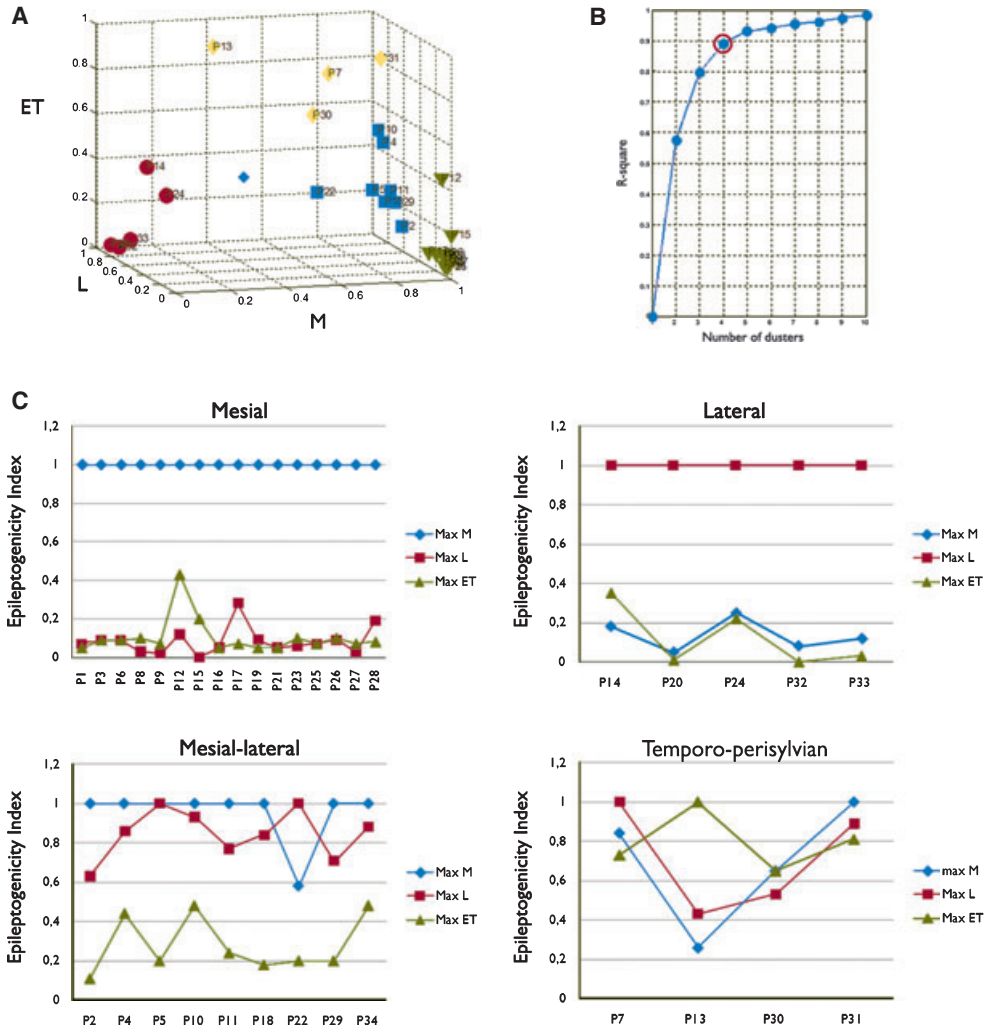

Figure 2.

(**A**) 3D representation of the EI values and the clustering performed using four classes by the *k*-means algorithm. Green, mesial (M) seizures; blue, mesial-lateral (ML) seizures; yellow, temporoperisylvian seizures (TPS); red, lateral (L) seizures. N = 34 patients. (**B**) Evolution of the *R*-square criterion (ratio of the intercluster inertia to the total inertia) with respect to the number *k* of clusters. The optimal number of clusters was obtained for $k = 4$ clusters (red circle). (**C**) Profiles of epileptogenicity in the four subtypes according to maximal values of EI obtained in mesial structures (M), lateral structures (L), or extratemporal cortices (ET).

included five patients with high lateral values (1) and low mesial values (0.05–0.25), defining thus the group of pure lateral TLE seizures (L group).

A third group included nine patients with high values in mesial structures (range 0.58–1) and in lateral structures (range 0.66–1) corresponding to previously defined mesiolateral seizures (ML group).

A last group of four patients was mainly characterized by high extratemporal values (0.65–1). This group of 4 cases mostly with prominent "extratemporal" cortex involvement and will be subsequently referred to as the temporoperisylvian subgroup of temporal lobe seizures (TPS).

Figure 2a depicts the four subgroups as classified by the *k*-means method and Fig. 2B illustrates the four classified subtypes according to the maximal EI values in M, L, and ET structures. Individual and detailed profiles of epileptogenicity (i.e., EI values versus explored structures) are plotted in Fig. 3. We see that the M group is characterized by epileptogenicity confined to mesial structures, whereas the L subtype is characterized by seizures that prominently involve the superior temporal gyrus. ML and TPS profiles are more complex, with epileptogenicity not confined to one sector of the temporal lobe.

Figure 4 shows typical examples of SEEG recordings in TLE seizures subgroups.

EI profiles in mesial structures in patients with M versus ML seizures

M and ML seizures were found to be the two groups with highest numbers in the selected population. ML seizures involved mainly the anterior mesial and neocortical regions of the temporal lobe, with variable EI values in extratemporal cortices (see Figs 3 and 4). They differ from seizures of the mesial group mainly in the extent of epileptogenicity to neocortical structures. We investigated whether differences between epileptogenicity of the mesial structures could also be a characteristic of this subtype. We finally found that mesial structures disclosed different patterns of epileptogenicity in these two subgroups of patients (Fig. S1a). ANOVA with interactions between values in mesial structures and subtypes (M or ML) disclosed very significant values ($F = 4, 23$; $p = 0.003$).

Indeed, in the pure mesial (M) group, high values were observed in the anterior hippocampus and to a lesser extent in the entorhinal cortex. In the ML group, the profile disclosed less marked involvement of the hippocampus,

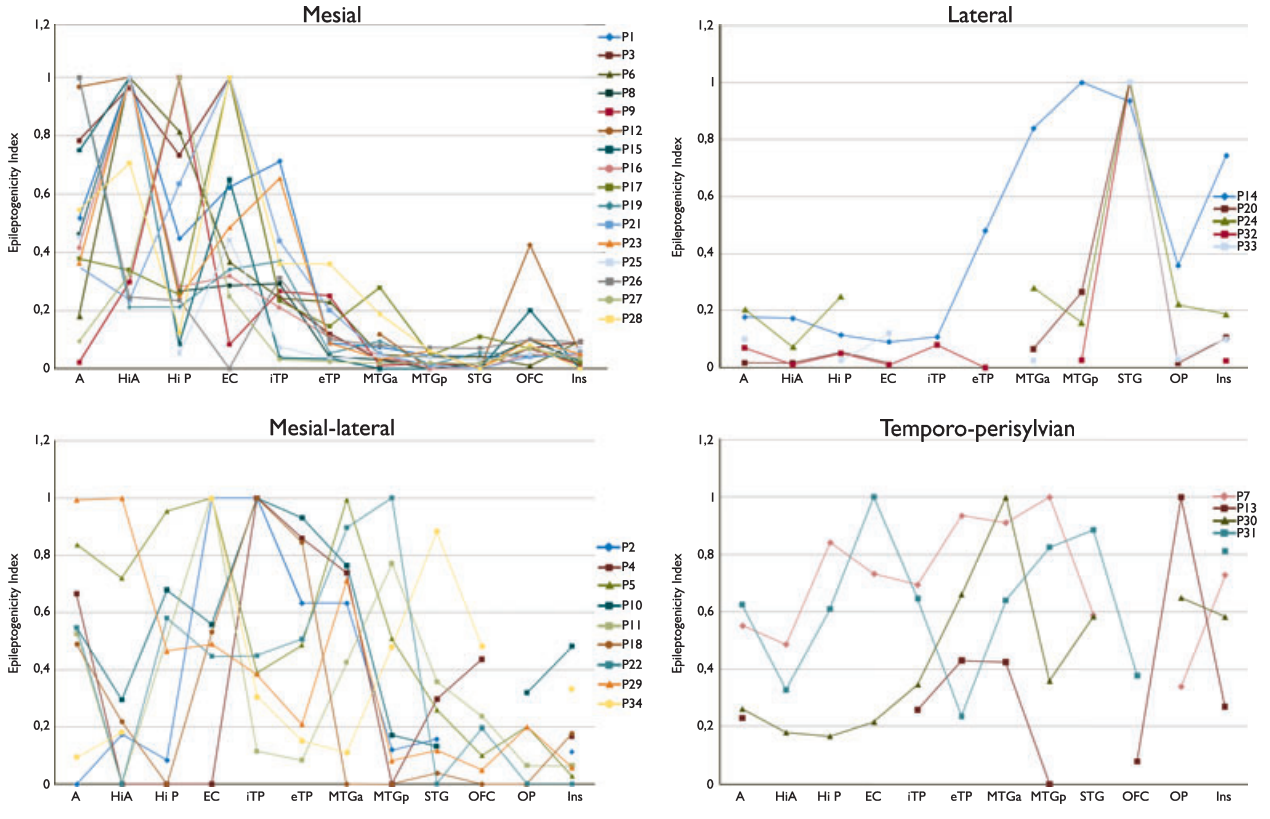

Figure 3.
Individual profiles of epileptogenicity. EI values are plotted for each patient and for each studied structure. M, Mesial; L, lateral; ML, mesiolateral; TPS, temporal perisylvian.
Epilepsia © ILAE

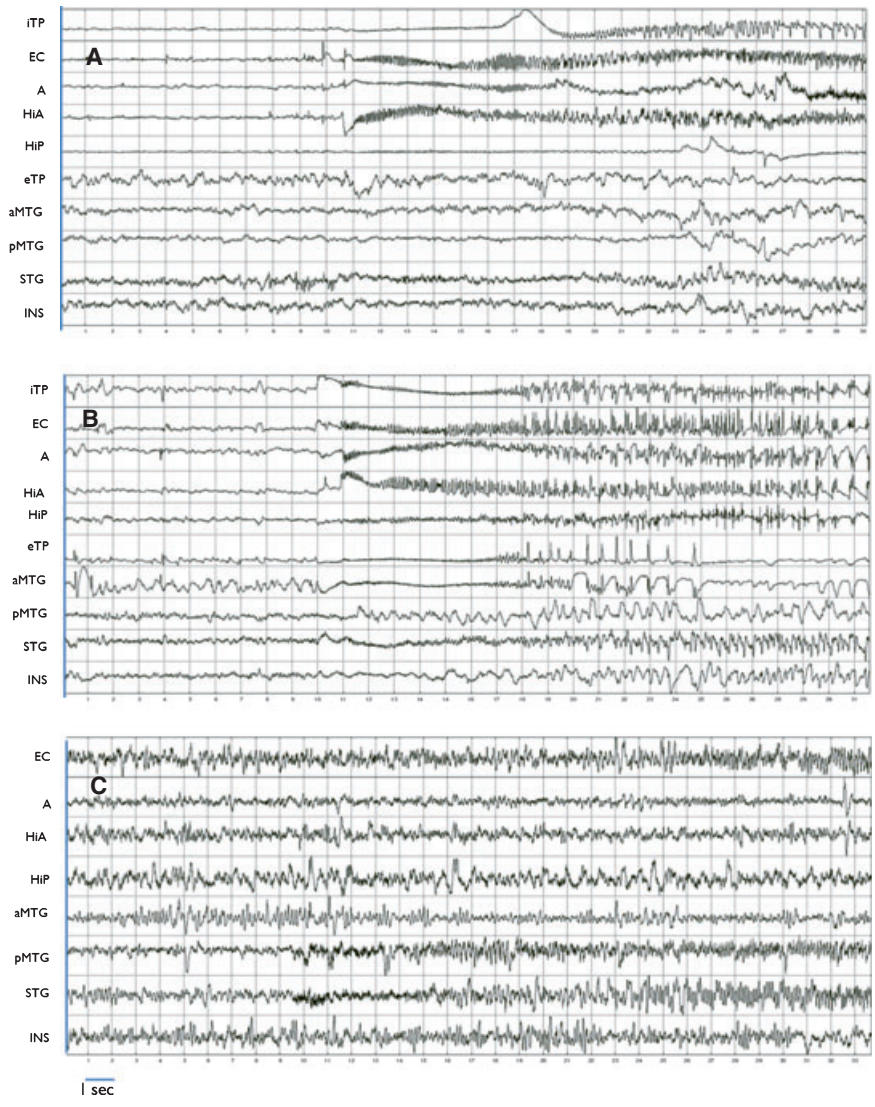

Figure 4.
Examples of SEEG recordings showing the main studied structures in three patients with (**A**) mesial seizure, (**B**) mesiolateral seizure, and (**C**) lateral seizure. For abbreviations see also Fig. 1. STG, superior temporal gyrus; INS, insula. Example of TPS seizure is shown in Fig. 1.
Epilepsia © ILAE

whereas extrahippocampal structures (EC and tPi) appeared to be more epileptogenic. Differences are significant for HiA ($p = 0.02$) and iTP (0.004). Taken as a whole this result suggests that the epileptogenicity seems to be more linked to extrahippocampal structures in the ML group and to hippocampus in the M group.

Relationship between TLE subtype and etiology

We have seen in the previous sections that TLE seizures may be divided into several subtypes. Another important issue is to investigate whether these subtypes are linked to different etiologies. We found that M subtypes are predominantly associated with HS, whereas ML subtypes are frequently associated with normal MRI or a lesion other than hippocampal sclerosis (HS; $p = 0.02$, chi-square). Figure S1b shows the distribution of the four subtypes according to underlying pathology, separated into HS, lesion other than HS (neurodevelopmental tumors, focal cortical dysplasia, and so on), or normal MRI (N). In addition, patients with normal MRI tended to have a greater number of EI ≥0.3 than patients with lesion or HS ($p = 0.07$).

Structure of the EZ: focus or network? Relation to duration of epilepsy

The structure of the EZ in the studied patients was analyzed. Schematically the EZ may be potentially organized as a simple focus (e.g., one structure is epileptogenic and initiates seizures that can subsequently spread to close or distant areas) or as a network of several anatomically distinct structures (e.g., two or more structures are conjointly involved into the generation of seizures). To this aim we determined, for each patient, the number of explored brain structures disclosing EI ≥0.3, a value previously defined as a good cutoff for determining potential epileptogenicity of the structure in TLE (Bartolomei et al., 2008a). This number will be denoted by $N_{EI \geq 0.3}$.

In the selected population the median number of epileptogenic structures was four. Figure 5 shows histograms in which patients from each subtype are separated according to the number of brain structures disclosing EI ≥0.3($N_{EI \geq 0.3}$). Only four patients disclose only one epileptogenic structure. Three of them belong to group L, and in these cases epileptogenicity was limited to the superior temporal gyrus. The other patient with only one $N_{EI \geq 0.3}$ had mesial seizures.

This result confirms that most TLE manifests a network organization of the epileptogenic zone. We then looked at whether there was a relationship between epilepsy duration and the extent of the EZ. The underlying hypothesis is that the development of epileptogenic networks is progressive with time and probably due to secondary epileptogenesis processes.

A nonparametric Spearman correlation found no correlation between age at epilepsy onset and $N_{EI \geq 0.3}$ (p = 0.85). In contrast we found that the duration of epilepsy was correlated with $N_{EI \geq 0.3}$ (Rho = 0.35, p = 0.04). As illustrated in Fig. 6B there was a positive trend between epilepsy duration and the number of epileptogenic structures.

Extratemporal involvement in patients with temporal lobe epilepsy

Using the automatic classification approach, four patients were clearly differentiated by the presence of highest EI values in extratemporal cortices. The profile of epileptogenicity of these patients is depicted in Figs 2B and 3. An example of epileptogenicity distribution is illustrated in Fig. 4D. However, it is noteworthy that some patients (mainly with ML seizures) also disclosed high EI values ($N_{EI \geq 0.3}$) in extratemporal cortices (Table S1). For example patients 10 and 12 had relatively high values in the extratemporal cortices (respectively, from orbitofrontal cortex and insuloopercular cortex). This finding is illustrated in Fig. 6A in which patients are classified according to maximal EI in extratemporal cortices. The last four patients are those classified as "TPS," but a gradual transition from patients with lower values to patients with the highest values can be observed. These findings strongly suggest that there is no absolute cutoff between TPS seizures and the other subtypes, in particular ML patients, but rather a gradual scale.

Relationship between TLE subtype and surgical prognosis

We examined whether EI values from either M or L or ET regions were correlated with surgical outcome. Seizure-free ("SF," Engel class I) patients and patients who were not rendered seizure free after surgery ("not SF") were compared using a nonparametric Mann-Whitney test. Surgical outcome is indicated in Table 1; 9 (32%) of 28 patients were not seizure free (Engel class II, III, or IV) after surgery.

Several parameters of the EZ were compared between "SF" and "not SF" patients. We first compared the maximal

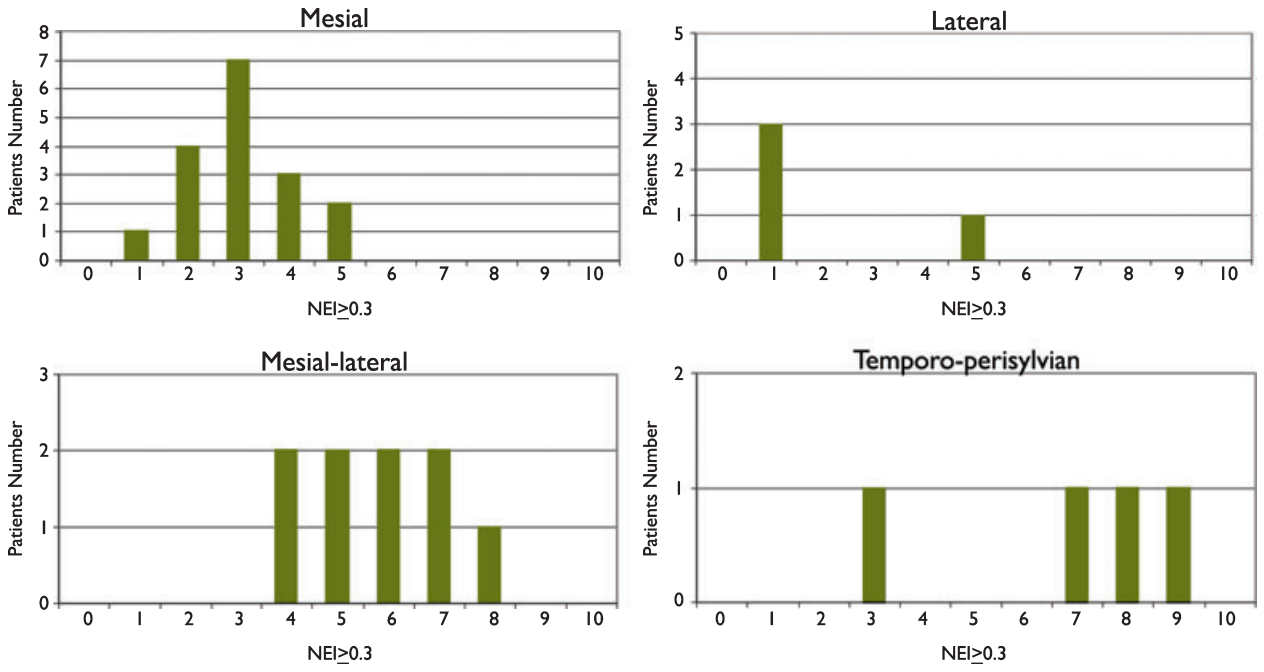

Figure 5.
Histograms showing the number of patients disclosing high EI values ($N_{EI \geq 0.3}$) in each subgroup. Only four patients disclose only one epileptogenic structure (one in M group and three in L group).
Epilepsia © ILAE

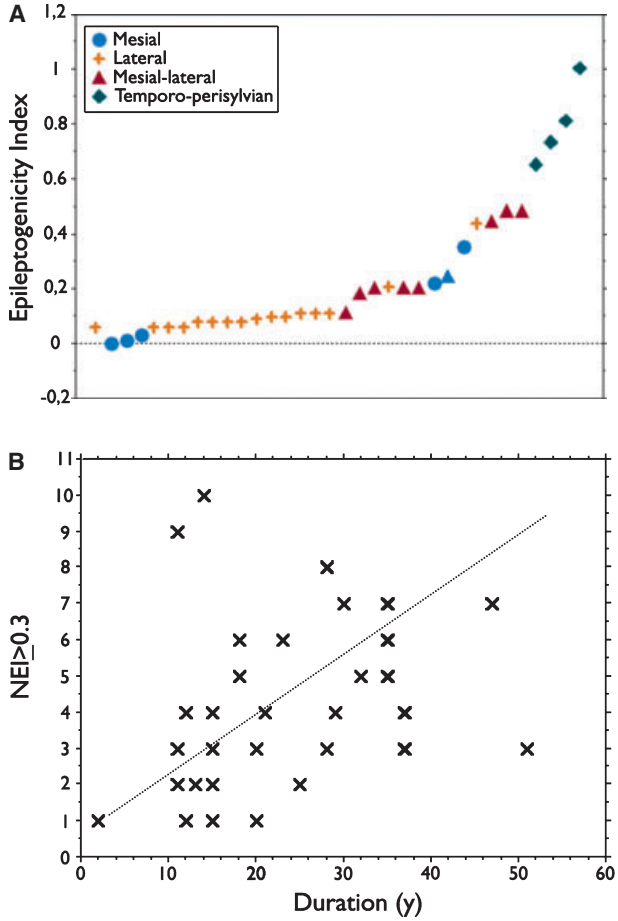

Figure 6.

(**A**) Maximal EI values obtained in extratemporal cortices in the 34 patients are indicated by ascending order and according to the corresponding subtypes. We notice that TPS patients have the highest values. Relatively high values are also observed in other patients, in particular from the ML group. (**B**) Relationship between the number of structures disclosing an EI value ≥0.3 ($_{NEI \geq 0.3}$) and the duration of epilepsy in the 34 studied patients.

EI values obtained in M, L, or ET cortices. M values were not different between the ''not SF'' group (0.80 ± 0.1) and the ''SF'' group (0.91 ± 0.03) (p = 0.52). L values were also not significantly different between the two groups (SF 0.38 ± 0.17, not SF 0.55 ± 0.18; p = 0.57). In contrast, ET values were found to be significantly higher in the ''not SF'' group (0.39 ± 0. 7) than the ''SF'' group (0.11 ± 0.07) (p = 0.01).

We then examined if the size of the epileptogenic zone was correlated with prognosis by comparing the number of IE >0.3 in the two groups. We found that the ''SF'' group exhibited a lower number of epileptogenic structures (3.3) than the ''not SF'' group (5.6) (p = 0.04).

Discussion

The main objective of this study was thus to quantify the brain structures (temporal cortices and adjacent cortices) involved in the generation of TLE seizures. In the present article, the involvement of temporal lobe as well as extratemporal lobe structures has been ''quantified'' using a mathematical quantity, the ''epileptogenicity index,'' EI. The proposed quantity is based on a typical electrophysiologic pattern (''rapid discharge'' or ''high frequency epileptiform oscillations'') recognized as a characteristic marker of the onset of focal seizures (Allen et al., 1992; Alarcon et al., 1995; Wendling et al., 2003; Worrell et al., 2004; Jirsch et al., 2006).

The index accounts for two main factors: the signal energy in well-defined frequency bands (appearance of β–γ oscillations concomitantly with the attenuation of slower α–θ oscillations) and the time at which rapid discharges occur. The combination of these two factors in a single quantity provides a good characterization of the epileptogenicity of explored brain structures (Bartolomei et al., 2008a; Aubert et al., 2009).

In this subset of patients, TLE seizures have been classified into four groups, including the two classically defined mesial and lateral types of TLE seizures, with the addition of two other forms. Mesial seizures were found to be the most frequent. This group was mainly defined by epileptogenicity confined to the mesial structures but with variable involvement of the different mesial regions (Bartolomei et al., 2008a). Etiology of this subgroup mainly includes patients with hippocampal sclerosis or normal MRI. The ML group has previously been proposed according to visual and coherence-based (Bartolomei et al., 1999) or nonlinear correlation-based (Bartolomei et al., 2001; Wendling et al., 2001) analysis of SEEG signals. This subtype of seizure is due to an EZ including both mesial and lateral parts of the temporal lobe. We found that ML subtypes are more frequently associated with lesional TLEs, a result in agreement with previous reports (Maillard et al., 2004; Usui et al., 2008). In contrast, this subtype is rarely associated with HS. Interestingly, patients with pure lateral seizures (L) are mainly characterized by an EZ restricted to the region of the superior temporal gyrus (STG). These posterior areas of the temporal lobe include primary (STG) or first-/second-order associative sensory areas for auditory, visual, or language functions (Pandya, 1995; Gloor, 1997) and have few direct limbic connections. This may explain the fact that the EZ may stay confined to neocortical structures. In contrast, in the ML subtype, the epileptogenic networks involve anterior neocortical structures, including associative cortex that have dense direct bidirectional connections with limbic structures, a potential argument for the development of epileptogenic networks in both medial and neocortical structures in this subgroup. The TPS group includes patients with EZ, including both temporal lobe structures and at least one

perisylvian cortex. In the present series, four patients were classified in this group according to the highest values measured in the adjacent ''extratemporal'' cortices. Additional epileptogenicity was present according to these measures in the opercular-insular cortices and/or orbitofrontal region. Interestingly, these seizures include regions closely anatomically connected to the anterior temporal regions (Augustine, 1996; Barbas, 2007; Insausti & Amaral, 2008) and represent well known anatomofunctional entities (Mesulam & Mufson, 1982).

Taken as a whole, our results are supportive of the concept of an ''epileptogenic network'' rather than that of restricted epileptic foci, since a majority of patients are shown to have several epileptogenic structures including not only the lesional site but also other distinct and distant sites (Bartolomei et al., 2008a,b).

As we previously found with MTLE (Bartolomei et al., 2008a), we have observed a relationship between the duration of epilepsy and the extent of the epileptogenicity, even if the relation is weaker in the whole group of TLE than in the previously studied MTLE group. Nevertheless, this finding advocates for a progressive recruitment of epileptogenic structures in human brain. The development of secondary epileptogenesis is probably an element of this process. According to this mechanism, recurrent epileptic activity in one structure can induce neurobiologic changes in distant structures of a neural network and finally provoke an extension of the epileptogenic network (Morrell, 1989; Sutula, 2001; Wilder, 2001).

Even if there is no doubt that TPS constitute part of the TLE population explored in presurgical evaluation, our study shows that the involvement of extratemporal cortices may also be relatively important in other subtypes. As previously proposed (Bartolomei et al., 2008a), the epileptogenicity in chronic drug-resistant TLE probably follows a gradient from the most to the least epileptogenic brain regions. Consequently, one of the most important problems in terms of surgery is to adequately determine the limit of the EZ. Inadequate resection size in terms of the extent of epileptogenicity has long been proposed to be a determining factor in surgical outcome. Our study corroborates this notion, since surgical outcome was correlated with the EI values in extratemporal cortices and the size of the EZ. To our knowledge, this is the first formal direct demonstration of this important notion, although indirect evidence was provided by studies reporting the poor surgical outcome of patients with ''palliative surgery''(Kinay et al., 2004; Wheatley, 2006) or with insular involvement (Isnard et al., 2000). This result is in agreement with a recent SEEG study showing that the involvement of insular cortex is associated with less favorable outcome in TLEs (Afif et al., 2008). The extension of epileptogenicity to surgically inaccessible regions, or to regions with particularly high functional risk for surgery such as the insular cortex or the left operculofrontal cortex, appears thus to be an insurmountable obstacle for currently used traditional surgical approaches. Use of alternative techniques alone or in combination with conventional surgery, such as deep brain stimulation (Boex et al., 2007; Velasco et al., 2007), electrothermocoagulation (Guenot et al., 2004), or radiosurgery (Regis et al., 2002) might be of help in these situations, but more investigation in this context is required.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. (a) Mean EI values and standard deviations measured from mesial structures in patients with mesial (blue) or mesiolateral seizures (red). (b) Etiology according to the subtype (M, L, ML, TPS).

Table S1. Values of the epileptogenicity index (EI) computed from structures of the temporal lobe and extratemporal cortices in 34 patients (P1–P34).

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