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The role of corticothalamic coupling in human temporal lobe epilepsy

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The EEG activity of the thalamus and temporal lobe structures (hippocampus, entorhinal cortex and neocortex) was obtained using intracerebral recordings (stereoelectroencephalography, SEEG) performed in patients with TLE seizures undergoing pre-surgical evaluation. Synchrony was studied using a statistical measure of SEEG signal interdependencies (non-linear correlation). The results demonstrated an overall increase of synchrony between the thalamus and temporal lobe structures during seizures. Moreover, although there was great inter-individual variability, we found that values from seizure onset period were significantly higher than values from the background period ($P = 0.001$). Values at the end of seizure were significantly higher than values from the seizure onset ($P < 0.0001$). Several indices were also defined in order to correlate some clinical features to the degree of coupling between cortical structures and the thalamus. In patients with mesial TLE seizures, a correlation was found between the degree of thalamocortical synchrony and the presence of an early loss of consciousness but not with other clinical parameters. In addition, surgical prognosis seemed better in patients with low values of thalamocortical couplings at the seizure onset. This report demonstrates that the thalamus and remote cortical structures synchronize their activity during TLE seizures and suggest that the extension of the epileptogenic network to the thalamus is a potential important factor determining surgical prognosis.

Keywords: temporal lobe; epilepsy; partial seizures; signal processing; thalamus

Abbreviations: EC = entorhinal cortex; ES = end of the seizure; ETSI = early thalamic synchrony index; GTSI = global thalamic synchrony index; Hip = hippocampus; MLSI = mesial–lateral synchrony index; MS = middle part of the seizure; MTLE = mesial temporal lobe epilepsy; NC = neocortical temporal cortex; SD = standard deviation; SEEG = stereoelectroencephalography; SO = seizure onset; TLE = temporal lobe epilepsy.

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Introduction

Temporal lobe epilepsy (TLE) is a form of partial epilepsy in which seizures originate primarily from the temporal lobe. Commonly, seizures arise from one or several anatomical divisions of the temporal lobe and propagate through interconnected neuronal networks limited to or extending beyond the boundaries of the temporal lobe. TLE is often drug-resistant, and in some cases surgery can be offered to stop the seizures, or to significantly reduce their frequency. In order to do that the 'epileptogenic zone' should theoretically be removed. Thus, to offer an appropriate surgical resection, it is crucial to better understand the brain networks involved during seizure activity. The anatomy of mesial TLE (MTLE), the most frequent subtype, has been particularly studied from human EEG recordings as well as from animal studies using induced temporal lobe seizures. It has been shown that MTLE seizures are generated within a network of mesial temporal lobe structures. However, structures outside the temporal lobe might also play a role in MTLE seizures. A potentially important extratemporal structure that could be involved early in the temporal organization of MTLE seizures is the midline thalamus. The role of synchronized thalamocortical oscillations has been well demonstrated

in animal models of absence seizures (McCormick and Contreras, 2001; Meeren *et al.*, 2002). During partial seizures, the role of such interactions has been less studied. Electrophysiological recordings have shown that midline thalamus may be involved early in spontaneous seizures of chronic epileptic rats (Bertram *et al.*, 2001). It has thus been suggested that the thalamus could act as a seizure amplifier and synchronizer of the ictal activity. Previous studies on thalamic involvement during human partial epilepsies have mainly focused on structural or metabolic imaging. Quantitative MRI studies have shown a decrease in volume of the ipsilateral thalamus in patients with TLE (DeCarli *et al.*, 1998; Dreifuss *et al.*, 2001; Bernasconi *et al.*, 2003; Natsume *et al.*, 2003; Bonilha *et al.*, 2004). Metabolic PET studies have also demonstrated a reduction in metabolic activity extending from the temporal lobe to the ipsilateral thalamus (Khan *et al.*, 1997; Juhasz *et al.*, 1999; Newberg *et al.*, 2000; Benedek *et al.*, 2004).

However, although these studies demonstrated that some partial seizures in humans are likely to involve anatomically connected regions of the thalamus, direct recordings and analysis of discharges in the thalamus have not previously been analysed in detail in partial epilepsy. Thus, the purpose of this work was to study thalamic activity during TLE seizures [using intracerebral recordings, stereoelectroencephalography (SEEG)], to analyse the synchronization between signals from temporal lobe structures and the thalamus and to correlate thalamic involvement with clinical parameters and surgical prognosis.

Methods

Patient selection and SEEG recording

Thirteen patients undergoing pre-surgical evaluation of drug-resistant TLE were selected among a series of 82 patients in whom intracerebral recordings have been performed. All patients had a comprehensive evaluation including detailed history and neurological examination, neuropsychological testing, routine MRI, surface EEG and SEEG (depth electrodes). SEEG was carried out as part of our patients' normal clinical care, and they gave informed consent in the usual way. Patients were informed that their data might be used for research purposes.

Clinical data and post-surgical outcome of these patients have been already reported (Maillard *et al.*, 2004). The ILAE surgical outcome classification (Wieser *et al.*, 2001) was used to assess post-surgical outcome.

Patients were retrospectively selected for the present study if they satisfied the following criteria: (i) seizures involved the temporal lobe at the onset; (ii) at least one orthogonal intracerebral electrode explored the thalamus. SEEG recordings were performed using intracerebral multiple contact electrodes (10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracranially according to Talairach's stereotactic method (Talairach *et al.*, 1992). A pre-planning of the implantation was performed on 3D T_1 MRI images using an original software (Regis *et al.*, 2005) for surface-rendering calculation, cortical anatomy analysis and sulci labelling (for more details, *see* http://brainvisa.info). Video EEG recording was prolonged as long as necessary for the recording of several usual seizures of the patient. 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 1.5 T). Finally, CT-scan/MRI data fusion was performed to anatomically check the location of each contact along the electrode trajectory according to previously described procedures (Bartolomei *et al.*, 2004). For the precise location of the contacts in the thalamus, both Talairach (Talairach and Tournoux, 1988) and Shaltenbrand (Schaltenbrand and Wahren, 1977) atlases were used. Several distinct functional regions of the temporal lobe can be explored via an orthogonal implantation of depth electrodes (Maillard *et al.*, 2004). All the patients had electrodes that spatially sampled mesial/limbic regions [amygdala, entorhinal cortex (EC) and hippocampus (Hip)] and lateral/neocortical regions of temporal lobe. Most of the patients had electrodes exploring extratemporal regions (prefrontal lobe and parietal cortex) to determine the way of propagation of the seizures.

The exploration of the thalamus was not a primary objective except in two cases with a lesion affecting both the thalamus and mesial temporal structures (Table 1). For the remaining patients, thalamic recording (mainly the medial pulvinar group or the posterior part of the dorsomedian nucleus) was derived from the most internal leads of the single multi-contact electrode clinically required to explore the superior temporal gyrus and the posterior temporo-operculo-insular regions thought to be potentially involved in the epileptogenic zone. Therefore, in these patients, no electrode was specifically implanted to record the thalamus in addition to those required by the diagnostic SEEG procedure (Fig. 1). Thus, the patients included in this study have been retrospectively selected on the basis of the presence of this type of electrode implanted for clinical purpose. Signals were recorded on a 128 channel Deltamed^{TM} system. They were sampled at 256 Hz and recorded on a hard disk (16 bits/sample) using no digital filter. Two hardware filters are present in the acquisition procedure. The first is a high-pass filter (cut-off frequency equal to 0.16 Hz at −3 dB) used to remove very slow variations that sometimes contaminate the baseline. The second is a first-order low-pass filter (cut-off frequency equal to 97 Hz at −3 dB) to avoid aliasing.

Table 1 provides clinical information about the patients selected for our study.

Procedure: SEEG signal analysis

Definition of regions and periods of interest

In this study, we specifically analysed the synchronization of bipolar signals (derived from two contiguous leads of the same electrode) between regions of interest. The regions considered were standardized and corresponded to two mesial temporal regions (Hip and EC), the neocortical temporal cortex (NC, corresponding to the middle temporal gyrus in patients with MTLE and to the superior temporal gyrus in patients with lateral TLEs) and the thalamus. The choice of the two leads in each region of interest was standardized as follows. As regards the Hip, EC and thalamus, we systematically chose the two most internal leads of three standard orthogonal electrodes exploring, respectively, (i) electrode 1: the head of the Hip by its internal leads and the middle temporal gyrus by its external leads; (ii) electrode 2: the EC by its internal leads and the middle temporal gyrus by its external leads; and (iii) electrode 3: the thalamus by its internal leads and the superior temporal gyrus on its external leads. As regards the NC, we

Table 1 Clinical data of patients included in the study

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years)	33	32	14	24	22	17	36	36	35	41	23	43	43
Gender	F	M	F	M	M	M	F	M	F	F	M	F	M
Age at onset (years)	3	17	3	3	12	5	16	18	3	15	13	32	8
Epilepsy duration (years)	30	15	11	21	10	12	20	18	32	26	10	11	35
Aetiology	Unk	CD	HS	OGD	As	HS	HS	Unk	CD	HS	CD	Encephalitis	Unk
MRI	Normal	CD left MTL	Left HS	OGD left MTL and thalamus	As right MTL	Left HS	Right HS	Normal	CD right MTL and thalamus	Right HS	CD first temporal gyrus	Normal	Normal
Aura	Deja vu	Anxiety, olfactive	no	Cold, shiver	Deja vu	No	no	Anxiety	Epigastric, cold	Nausea, disgust, anxiety	Auditory	Auditory	Auditory
Early loss of contact	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes
Secondary generalization	Rare	Frequent	No	Frequent	Rare	Rare	Rare	Rare	Rare	Rare	Rare	Rare	Frequent
Seizure onset	Me	Me	Me	Me	MeL	Me	Me	MeL	Me	Me	Nc	Nc	Nc
Type of TLE	L-MTLE	L-MTLE	L-MTLE	L-MTLE	R-MLTLE	L-MTLE	R-MTLE	L-MLTLE	R-MTLE	R-MLTLE	R-LTLE	R-LTLE	R-LTLE
Delay of TH involvement (s)	0	0	16	0	3	5	61	4	0	10	ni	ni	14
Seizure duration (s)	45	152	76	62	58	197	71	52	56	250	82	118	57
Type of surgery	ATL	ATL	ATL	ATL	ATL	ATL	ATL	NO	ATL	ATL	NCC	NO	NCC
Follow-up (years)	2	2	3	3	3	4	2	–	2	2	2	–	3
Post-surgical outcome (ILAE)	4	3	1	3	1	3	1	–	1	1	1	–	1

M = male; F = female; CD = mesial temporal cortical dysplasia; Unk = unknown; As = astrocytoma affecting the lateral temporal cortex; HS = hippocampal sclerosis; OGD = oligodendroglioma affecting mesial temporal structures; R = right; L = left; LTLE = lateral temporal lobe seizures; MLTLE = mesial–lateral temporal lobe seizures; MTLE = mesial temporal lobe seizures; TH = thalamus; seizure onset in Me = mesial strcutures, MeL = mesial and lateral neocortical structures and Nc = neocortical structures (superior temporal lobe gyrus); ni = not involved; NO = not operated; ATL = anterior temporal lobectomy; NcC = neocortical cortectomy.

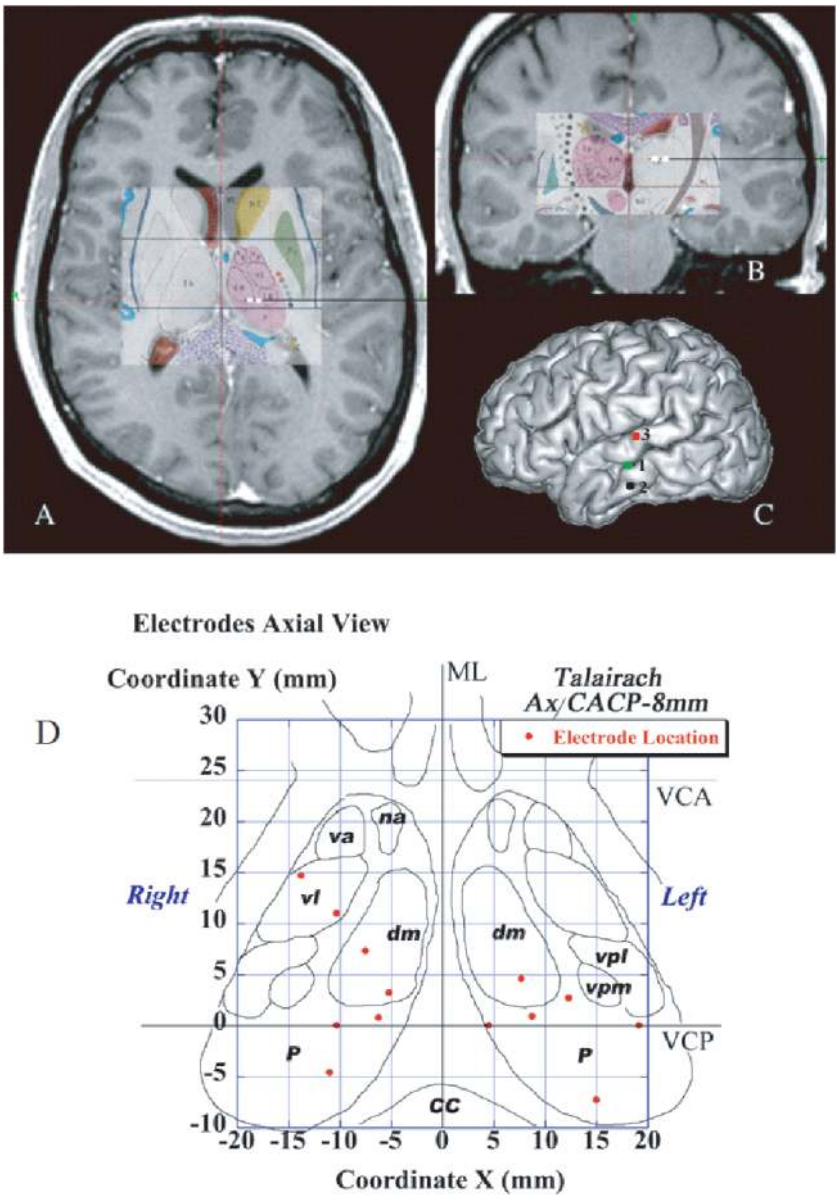

Fig. 1 Illustrative case no. 8. The electrode displayed here is entering the cortex of the superior temporal gyrus (T1) at the level of the left temporal transverse gyrus (TTG). In **A** the trajectory of the electrode is shown on the MR axial view superimposed with the Talairach atlas homologous slice. In **B** the trajectory of the electrode is visualized on a MR coronal view. In **C** the entry point (in red) of the electrode in the cortex of T1 is visualized on the surface rendering of the cortical mantle. The lateral leads of the electrode (**A** and **B**) are allowing the recording of the activity of the superficial cortex of T1, the cortex of the posterior TTG, the anterior TTG and then the insular cortex (posterior insular gyrus). The mesial leads (**A**) according to Talairach statistical atlas are located at the anterior part of the pulvinar nuclei complex close to the dorsomedianum and ventroposterolateral nuclei. The entry points of the electrodes recording the EC (electrode 2, black) at the internal contacts and the Hip (internal contacts) and the middle temporal gyrus (external contacts) (electrode 1, green) are also indicated. (**D**) Spatial distribution of the depth electrode thalamic contacts for the whole population studied. Each red dot is representing the equidistant point of the location of a pair of two contacts recording the bipolar activity from the thalamus, for each patient. These points are displayed on the Talairach atlas in the axial slice 8 mm above the ACPC line.

systematically chose the most external leads of the electrodes exploring the middle or superior temporal gyrus (i.e. electrode 1 or 3).

Four periods were defined in order to quantify the interactions between the four selected structures (Fig. 2).

Background (BKG): This period of background activity (duration of 20 s) was spaced at least 1 min apart from the onset of ictal discharge and was used as reference period in the analysis of correlations between signals.

Seizure onset (SO): We arbitrarily chose a duration of 10 s for analysis including 5 s before and 5 s after the appearance of a tonic discharge in mesial and/or neocortical structures. The rapid discharge that occurs at seizure onset was delimited by visual

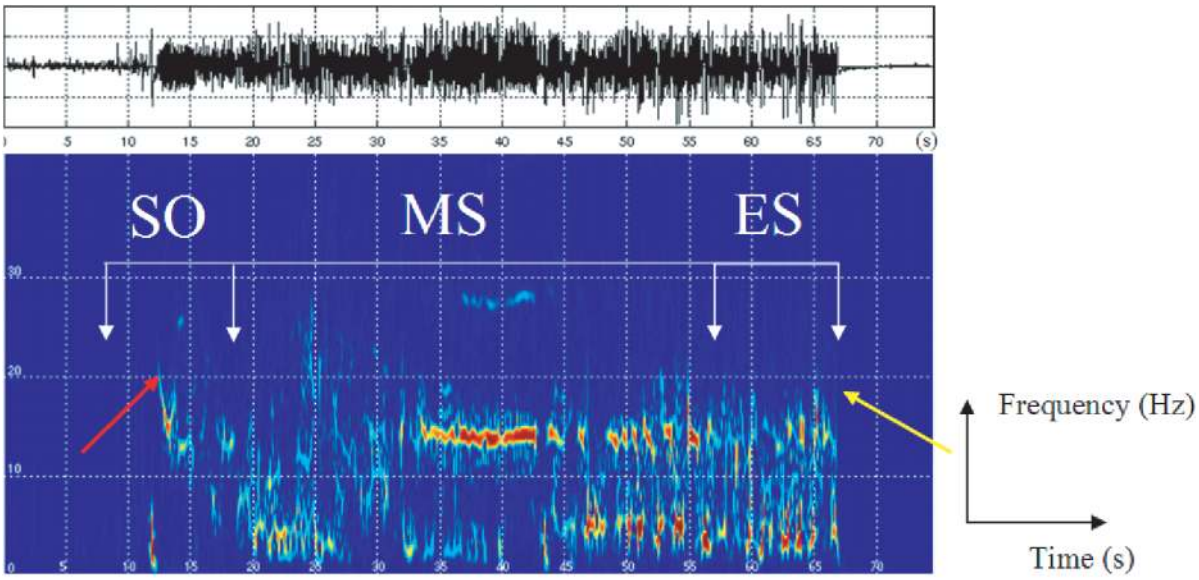

Fig. 2 Definition of the time–frequency (TF) representation of a seizure recorded in the Hip from a patient with mesial TLE. TF is used to reveal the high-frequency activity at the seizure onset (red arrow) and the end of rhythmic ictal activity (yellow arrow) recorded here in the Hip. The period SO (seizure onset) includes 5 s before and 5 s after the onset of high-frequency activity. The period ES (end of seizure) is defined as the last 10 s of the seizure. Period MS (middle of seizure) is the junction between these two periods.

inspection as well as on a time–frequency representation of signals [smoothed pseudo Wigner–Ville distribution (Wendling *et al.*, 1999)] that was used to accurately determine the beginning of the rapid activity, as illustrated in Fig. 2.

Middle part of the seizure (MS): Period separating the preceding from the following.

End of the seizure (ES): This period included the last 10 s of the seizure discharge.

Estimation of average correlations over periods of interest

Correlation between signals (or cross-correlation) recorded from the Hip, EC, NC and thalamus was estimated as a function of time by using non-linear regression analysis (Pijn and Lopes Da Silva, 1993). This analytical method may be used to measure the degree and direction of functional coupling between neuronal populations. Details of the method can be found in our previous studies (Wendling *et al.*, 2001; Bartolomei *et al.*, 2004). In brief, non-linear regression analysis provides a parameter, referred to as the non-linear correlation coefficient h^2, which takes values in the range [0, 1]. Low values of h^2 denote that signals X and Y are independent. On the other hand, high values of h^2 mean that signal Y may be explained by a transformation (possibly non-linear) of signal X, that is, signals X and Y are dependent. In addition to the estimation of h^2, a second quantity is evaluated that brings information on the causal property of the association. This quantity, referred to as the direction index D, takes into account both the estimated time delay τ between signals X and Y (latency) and the asymmetrical nature of the non-linear correlation coefficient h^2 (values of the h^2 coefficient are different if the computation is performed from X to Y or from Y to X). Values of parameter D range from -1.0 (X is driven by Y) to 1.0 (Y is driven by X).

Signals were sampled at 256 Hz; this consideration led to the choice of a length of 4 s for the analysis window sliding by steps of 0.25 s (Fig. 3). The h^2 values were averaged over each period of interest defined above, for each pair of signals and for each recording. In each patient, the two first seizures of the SEEG procedure were analysed. Figure 3 gives an example of correlation estimation between thalamic and hippocampic signals during a mesial temporal lobe seizure.

Statistical analysis

Statistical analysis first focused on h^2 values averaged over periods of interest in order to determine if significant differences exist in the evolution of correlation values. In order to test the hypothesis that h^2 values over three periods (SO, MS, ES) differ from background periods, a repeated-measure ANOVA (analysis of variance) was used. Fisher's test was used for multiple comparison.

In addition, in each patient, the correlation values from each ictal periods were standardized relative to the values obtained in the BKG period using a Z-score transformation. For individual analysis of h^2 values, a Z-score of +2.0 on mean h^2 values obtained in the ictal period indicates a value that is 2 SD (standard deviations) above the mean of background h^2 values and was considered significant.

In order to correlate the degree of synchronization and clinical variables including post-surgical outcome, we defined three indices. Two were aimed at describing the importance of thalamic involvement (in terms of spatial and temporal extent of the synchrony), and one at describing the interactions between mesial and lateral temporal structures.

The first was defined as the 'early thalamic synchrony index' (ETSI) and was calculated for each patient as the sum of *Z-score* values for each thalamocortical interaction divided by the number of interactions during the first ictal periods (SO period). In the present paper, three interactions were calculated for each ictal period (thalamus-Hip, thalamus-NC and thalamus-EC). The second defined here as the 'global thalamic synchrony index' (GTSI) was

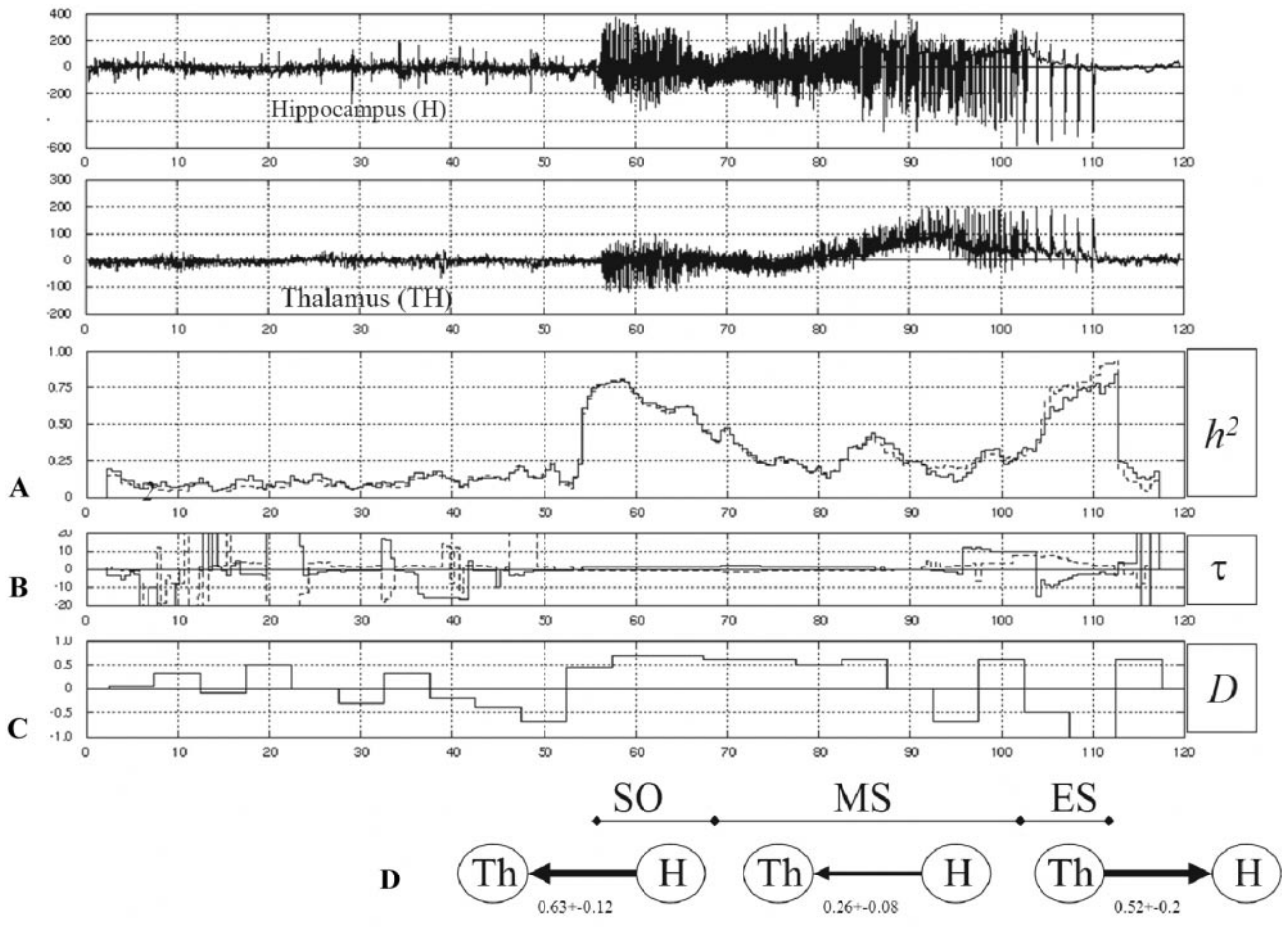

Fig. 3 Signal processing procedure used to characterize coupling between structures from signals they generate. On each pair of signals, non-linear regression analysis is used to compute (**A**) the non-linear correlation coefficient h^2 and (**B**) the time delay τ from upper signal to lower and asymmetry information (difference between h^2 coefficients), and time delays are jointly used to compute the direction index *D* that characterizes the direction of coupling (**C**). When >0 (respectively <0), *D* indicates a coupling from upper to lower signal (respectively lower to upper signal). (**D**) h^2 values are averaged over considered periods and information is represented as a graph in which line thickness is proportional to the average h^2 value and in which the arrow indicates coupling direction, when significant. Standard deviation of coefficient h^2 is also provided. In this case, a mesial seizure is analysed. A large increase in correlation is observed in the first period and the direction index *D* indicates that the mesial structure (H) is leader. The second period (MS) is characterized by the maintenance of a significant correlation and the *D* index also indicates that H is leader. The last period is characterized by a re-increase of h^2 values. *D* index values are now negative, indicating that the thalamus (TH) is now the leader structure.

the sum of *Z*-score values for each thalamocortical interaction divided by the number of interactions during the three ictal periods (i.e nine interactions). The third index defined as 'mesial–lateral synchrony index' (MLSI) was defined as the sum of *Z*-score values for each mesial–neocortical interaction (EC-NC and Hip-NC) divided by the number of interactions during the three periods (6 interactions). See an example in Table 2.

Non-parametric tests were used to study the correlations between clinical parameters and the synchrony indices.

Spearman's rank correlation coefficient was calculated to find possible correlations between the synchrony indices defined above and age at epilepsy onset, epilepsy duration and seizure duration. Influence of synchrony indices on surgery outcome [two groups were compared: patients seizure-free (i.e stage 1 ILAE classification) and patients not seizure-free] and on two clinical parameters (existence of secondary generalization and early loss of consciousness) was tested using the non-parametric Mann–Whitney test. A *P*-value < 0.05 was considered to be statistically significant.

Results

The main patient characteristics are summarized in Table 1.

Thalamic involvement during TLE seizures

The electrical onset of all seizures was characterized by the appearance of an ictal discharge in the lateral or/and

Table 2 Individual interactions between regions of interest during each period

		Patients												
Periods	Interactions	1	2	3	4	5	6	7	8	9	10	11	12	13
	H–EC	6.2 (EC)	3.39 (EC)	2 (H)	6.375 (BD)	2.9 (H)	0.8	2 (H)	1.2	3 (EC)	−0.8	−0.44	−0.42	0.50
SO	H–NC	−1.6	3.91 (NC)	−0.5	1.2	8 (NC)	0.2	−0.7	4.9 (H)	−0.5	0.3	−0.65	−1.50	1.72
Z-scores	H–Th	5.1 (Th)	1.1	0.3	2.42 (H)	2.3 (H)	0.6	−0.3	4 (H)	0.6	−0.2	1.08	−0.50	0.09
	EC–NC	0.5	3.25 (EC)	0.5	−0.1	0.6	−0.1	−1.7	−0.1	−0.1	0.1	−0.28	0.25	2.5 (NC)
	EC–Th	13.5 (EC)	4.83 (EC)	1.0	0.7	−0.5	1.4	−0.8	1.4	0.4	−1.8	−0.32	0.17	1.21
	NC–Th	0.4	5.0	0.7	1.2	6 (NC)	0.4	−1.0	2.3 (NC)	0.3	−2.5	1.58	0.13	3.12 (NC)
	H–EC	2.5 (H)	6.02 (EC)	4.25 (H)	4.12 (H)	0.6	4.1 (H)	−0.3	0.0	4.1 (H)	2.5 (H)	0.38	1.75	3.06 (EC)
MS	H–NC	−0.7	5.75 (NC)	2.17 (H)	−1.0	1.8	2.5	−1.4	2.8 (H)	−0.2	−0.3	−0.25	−1.17	1.98
Z-scores	H–Th	4.1 (H)	11.45 (H)	4.37 (H)	−0.1	3.4 (H)	4.9 (H)	−0.2	6 (H)	3.75 (Th)	0.1	0.75	−0.83	0.63
	EC–NC	0.3	4.43 (EC)	1.3	−0.3	−1.3	3 (EC)	−3.6	0.2	−0.4	0.4	1.20	0.25	0.58
	EC–Th	2.3 (EC)	10.45 (EC)	2.04 (EC)	2.16 (Th)	−2.3	4.6 (Th)	−2.4	3.3 (EC)	2 (EC)	1.8	0.25	0.75	0.34
	NC–Th	0.1	7.5	5.2 (NC)	−0.8	4.8 (NC)	1.6	−1.1	5.7 (NC)	1.8	−1.2	0.33	−0.63	0.25
	H–EC	4 (EC)	4.58 (EC)	5.12 (BD)	3.12 (H)	1.5	2.5 (EC)	6.6 (H)	−0.1	3.4 (H)	1.7	0.19	6 (BD)	7 (EC)
SE	H–NC	2.8 (H)	5.2 (NC)	2.71 (H)	2.33 (NC)	−0.8	−0.4	−0.6	1.1	1.1	4.25 (H)	−0.25	−0.83	1.90
Z-scores	H–Th	6.9 (Th)	14.33 (H)	6 (H)	1.6	2.2 (H)	1.2	0.4	2.2 (H)	5.2 (Th)	3.3 (H)	−0.33	−1.00	2.85 (Th)
	EC–NC	1.9	7.2 (NC)	2.37 (EC)	0.4	−0.1	0.1	−0.6	−0.4	1.3	0.6	−0.46	0.00	8.58 (EC)
	EC–Th	5.8 (Th)	15.83(EC)	3.91 (EC)	3 (Th)	2.5 (EC)	1.3	8.2 (EC)	3.5 (EC)	2.2 (Th)	9.25 (BD)	−0.86	0.00	2.87 (Th)
	NC–Th	1.7	18.4	5.58 (Th)	0.8	0.2	2.8 (Th)	−0.2	2.2 (NC)	1.8	6.16 (NC)	0.67	−0.13	12.8 (NC)
Indices	MLSI	0.54	4.95	1.42	0.42	1.37	0.87	−1.41	1.40	0.20	0.89	−0.11	−0.50	2.86
	ETSI	6.35	3.65	0.65	1.42	2.60	0.78	−0.70	2.58	0.40	−1.48	0.78	−0.07	1.47
	GTSI	4.44	9.89	3.23	1.20	2.07	2.08	0.29	3.42	2.00	1.66	0.35	−0.23	2.68

In each interaction, the *Z*-scores of h^2 value related to the background period is indicated. In the brackets is indicated the leader structure (according to the index of direction *D*) in the coupling when *Z*-score is >2. BD indicates a bidirectional coupling [see Bartolomei *et al*., (2001) for details about the determination of leader structure]. Positive *Z*-scores indicate an increase of correlation, and negative, a decrease of correlation. *Z*-scores were calculated from h^2 values averaged from two seizures. EC = entorhinal cortex; H = hippocampus; Th = thalamus; NC = neocortex. In the three last rows are indicated the values of three synchrony indices calculated from the *Z*-score values. MLSI = mesiolateral index, ETSI = early thalamic synchrony index, GTSI global thalamic synchrony index. For example, in Patient 1 the ETSI was (5.1 + 13.5 + 0.4)/3 = 6.35; the GTSI was [(5.1 + 13.5 + 0.4) + (4.1 + 2.3 + 0.1) + (6.9 + 5.8 + 1.7)]/9 = 4.43; and the MLSI was [(−1.6 + 0.5) + (−0.7 + 0.3) + (2.8 + 1.9)]/6 = 0.54.

mesial temporal structures. Seizures in three patients started from the lateral neocortex affecting mainly the superior temporal gyrus (lateral seizures, L). In three patients, seizures started simultaneously from lateral and mesial cortex (mesiolateral seizures, ML) and in seven patients the seizures started from the mesial region of the temporal lobe (mesial seizures, M). Signals recorded by electrodes sampling extratemporal lobe cortical regions did not show EEG modifications, indicating that these regions were not involved at seizure onset. Schematically and as illustrated in some examples in Fig. 4, three patterns of the thalamus involvement could be determined by visual inspection:

- a first group of four patients showed very early involvement of the thalamus. With visual analysis the seizures appeared to emerge simultaneously (within the first second) in the mesial temporal lobe and the thalamus (Patients 1, 2, 4 and 9).
- a second group of seven patients demonstrated delayed involvement of the thalamus varying from 3 to 61 s (Patients 3, 5, 6, 7, 8, 10, 13) (mean: 18 s ±22).
- a third group of two patients in whom no evident propagation to the thalamus was observed (Patients 11 and 12).

Correlation of signals from temporal lobe regions and thalamus

Non-linear correlation was calculated between pairs of bipolar signals from two mesial structures (EC and Hip), one neocortical region (NC) and the thalamus.

Figure 5A shows the mean and SD of all the interactions in each studied period. There was an overall increase of synchrony from the SO period to the end of the seizure. The maximal values of synchrony were observed during the last part of the seizure. Significant interaction between periods and h^2 values were found ($F = 21.1$, $P < 0.0001$).

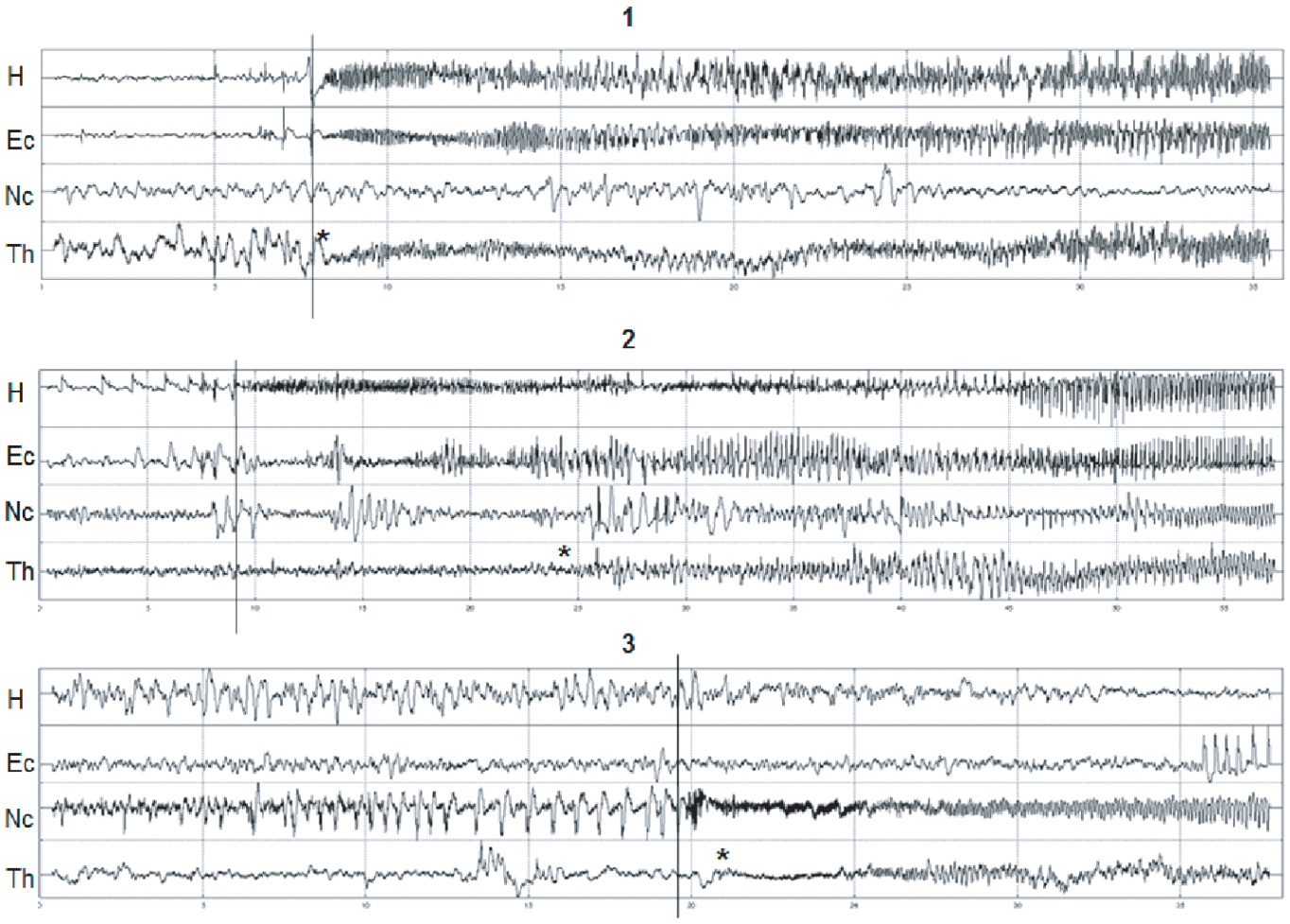

Fig. 4 Three SEEG recordings of seizures involving the temporal lobe structures and the thalamus. (1) Seizure starts with a tonic discharge simultaneously recorded in the mesial temporal structures and the thalamus (Patient 9). (2) Seizure starts in the mesial structures and secondarily spreads to the thalamus after 15 s (Patient 3). (3) Seizure starts from the neocortex and secondarily involves the thalamus (Patient 11). In this case the tonic discharge is preceded by a spiking activity. Ec: entorhinal cortex, H = hippocampus, Th = thalamus, Nc = neocortex. The bar indicates the onset of the tonic ictal discharge and asterisk the onset of thalamic discharge.

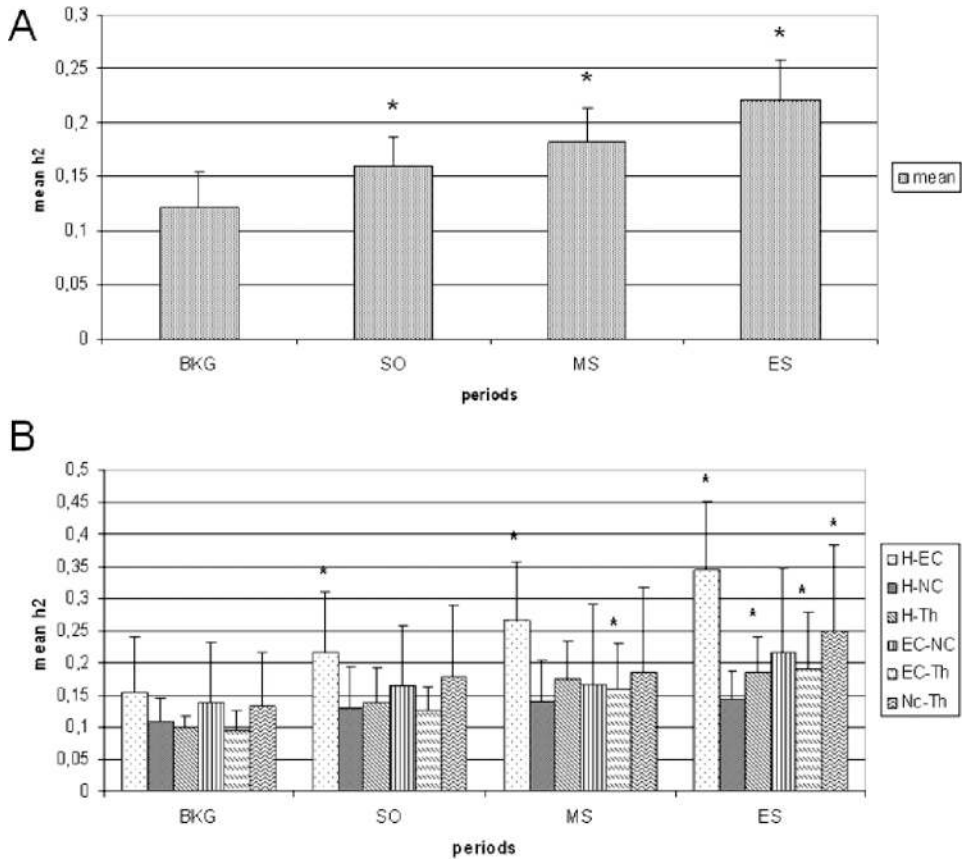

Fig. 5 Mean (and SD) values of h^2 during the three ictal periods. (**A**) Variation of h^2 values for all the averaged interactions. (**B**) Variation of h^2 values for each studied interaction. *Significant results relative to background period (ANOVA with Fisher's test for multiple comparisons).

Values from SO period ($P = 0.001$), MS period ($P < 0.0001$) and ES period ($P < 0.0001$) were significantly higher than values from the BKG period. ES values were significantly higher than values from SO and MS periods (respectively $P < 0.0001$ and $P = 0.009$).

Figure 5B shows in detail each interaction obtained from the 13 patients during the three periods. In particular, the SO period was characterized only by significant couplings within the temporal structures (in particular between Hip and EC, two regions forming the epileptogenic zone in the majority of patients). Significant interactions between the EC and the thalamus appear during the MS period. The ES period is marked by significant synchrony between mesial temporal structures and the thalamus and between thalamus and neocortex.

In contrast, during this period no significant coupling was observed between the neocortex and the mesial temporal structures.

Analysis of individual results and clinical correlations

In order to analyse individual results, a *Z*-score transformation was performed for h^2 values (averaged from the two seizures) of SO, MS and ES periods relative to the mean and SD of h^2 values measured in the background period.

The main results are summarized in Table 2. Figure 6 shows three examples of patients with significant early synchrony between the thalamus and temporal structures.

For most individual cases, no early significant corticothalamic interaction was noted. When early and significant interactions occurred between temporal lobe structures and the thalamus, the thalamic activity was in the majority of cases driven by the cortical activity (in Table 2, the leader structure is indicated in brackets for each significant interaction). This result indicated that during the first part of the seizure, the activity of the thalamus was driven by the temporal lobe structures. However, during the course of the seizure, the direction of the coupling may change. Only two patients (11–12) did not disclose significant corticothalamic interactions. These two patients had lateral temporal lobe seizures. In order to correlate the degree of synchronization and the clinical variables, we calculated three indices (*see* Methods). Values of ETSI, GTSI and MLSI are indicated in Table 2, showing a large range of values from one patient to another. Negative values indicated a tendency to a decoupling instead of a coupling between the studied brain regions.

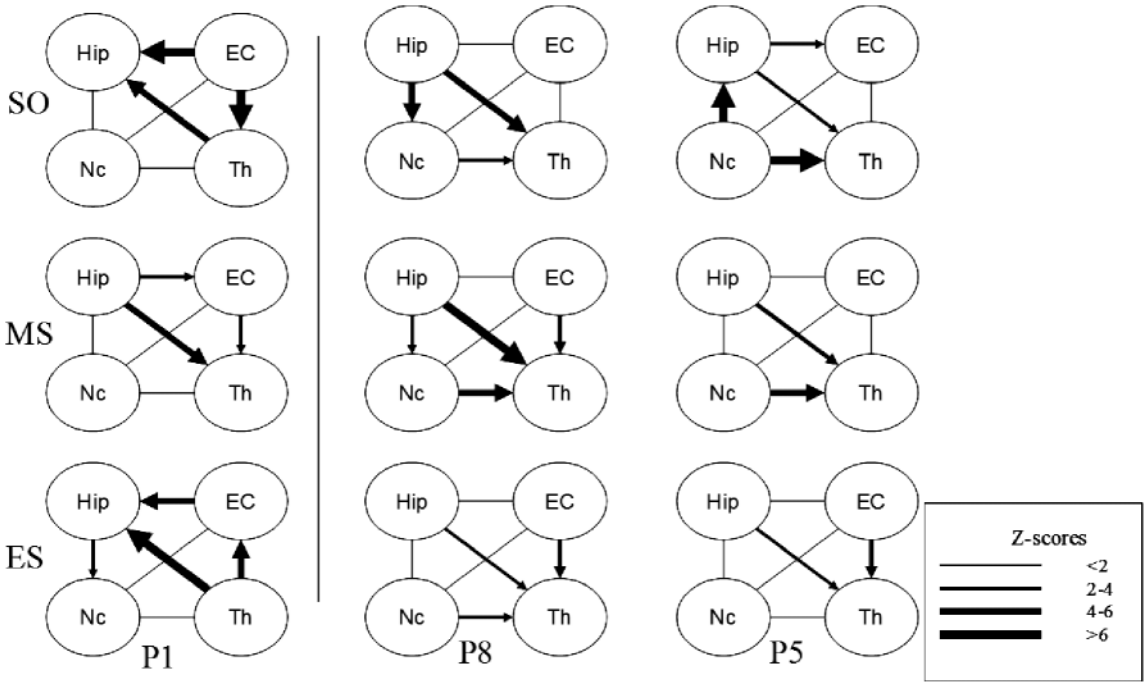

Fig. 6 Scenarios of thalamocortical and corticocortical couplings in three cases with early involvement of the thalamus. The three ictal periods are represented (SO = seizure onset, MS = middle part of the seizure, ES = end of seizure). Coupling between structures is indicated when significant increase is observed relative to the reference period (*Z*-scores > 2). Direction of coupling is based on the direction index *D* estimated from the non-linear correlation calculation.

Table 3 Main statistical results for correlations (*P*-values) between the three indices of synchrony and clinical/electrophysiological data

	Secondary generalization*	Loss of contact*	Age at onset**	Epilepsy duration**	Seizure duration**	Surgical outcome (SF versus not SF)*
GTSI	0.12	**0.001**	0.50	0.81	0.9	0.38
ETSI	0.17	**0.008**	0.35	0.9	0.1	**0.04**
MLSI	0.12	**0.01**	0.59	0.8	0.9	0.37

In bold: significant results ($P < 0.05$) after Mann–Whitney or Spearman's r correlation coefficient calculation. *Mann–Whitney, **Spearman's correlation.

These indices have been correlated to several clinical features in Table 3. No significant correlation was found between the synchrony indices values and the age at epilepsy onset, the duration of epilepsy or the seizure duration. No significant interaction was found between the rate of secondary generalization reported in the patient's history [rare versus frequent (>2/*y*)] and the three synchrony indices (MLSI, ETSI and GTSI). However, as none of the analysed seizures were secondary generalized, our data cannot directly demonstrate the potential direct relation between cortico-thalamic synchrony and secondary generalization during a seizure.

Conversely, significantly higher values of MLSI, ETSI and GTSI were found in patients with early loss of consciousness (within the first 10 s) during their seizure (MLSI $P = 0.01$; ETSI $P = 0.008$ and GTSI $P = 0.01$). In addition, a significant correlation was also found between ETSI (but not with GTSI) and the surgical results ($P = 0.04$). Mean ETSI was at 2.9 ± 2.1 in the not seizure-free group and at 0.45 ± 1.2 in the seizure-free group. It is interesting to note that the two patients with the highest ETSI had a poor outcome after anterior temporal lobectomy (Patients 1 and 2). No correlation was found between surgical results and MLSI values.

Discussion

Coupling of thalamocortical activities in TLE seizures

Our results show that epileptic activity may involve the thalamus during the course of seizures. Only two patients did not manifest obvious propagation to the thalamus, both of whom had lateral TLE.

Results of the quantification demonstrate that synchronization of signals from the thalamus and the temporal lobe

structures occurs during seizures and tends to be particularly constant and marked in the last phase of the seizure. These results corroborate the notion that synchronization loops between the thalamus and cortex take place during the course of partial seizures and may amplify the spreading of seizures, as has been suggested by animal studies (Bertram *et al.*, 2001). Thalamic involvement may occur early in the course of the seizure, as observed in some of our patients. Although we never observed a leader role for the thalamic region at the seizure onset, this result indicates that a large cortical and subcortical network of structures may be engaged at the beginning of the seizure. These results are in agreement with animal studies. In experimental models of TLE, the thalamus has been shown to be involved during the course of seizures (Bertram *et al.*, 2001) and may play a crucial role in seizure development (Cassidy and Gale, 1998).

The thalamus is constituted of many different nuclei with specific thalamocortical connections and we cannot determine whether the seizure activity was a part of a more widespread involvement of the thalamic nuclei. The pulvinar part of the thalamus, which is the main explored nucleus in our study, has many nuclear subgroups, and, schematically, the most medial–dorsal part is connected to associative cortices of the frontal, parietal and temporal lobe while the lateral–ventral segment has strong connections with extrastriate visual areas (Grieve *et al.*, 2000). To our knowledge, there is no study specifically dealing with its role in partial epilepsy. In animal models of temporal lobe seizures, the role of ventral midline thalamus has been more extensively described (Turski *et al.*, 1986; Clifford *et al.*, 1987; Bertram and Scott, 2000). In humans, metabolic and imaging studies have also found alterations predominant in the dorsomedian nucleus (Khan *et al.*, 1997; Benedek *et al.*, 2004). Since the medial pulvinar has many connections with associative cortices, it is also a structure that may serve as a relay for spreading the epileptic activity. In addition, the fact that its involvement is observed in all the seizures affecting the most associative parts of the temporal lobe (mesial structures, anterior temporal neocortex) is in agreement with its anatomical situation. Finally, the interactions between the thalamus and cortex as described in this paper might reflect a more widespread phenomenon affecting other thalamic nuclei. Our study also suggests that seizures arising from the superior temporal gyrus (lateral TLE) more rarely interact with the thalamus.

Clinical correlations

Animal studies have suggested a potential role for the thalamus in secondary generalization, since pharmacological manipulation in the midline thalamic nuclei significantly limits the rate of secondary generalization (Turski *et al.*, 1984). In addition, pharmacological inactivation of the thalamus by lidocaine shortened the discharge in the Hip in kindled rats (Bertram *et al.*, 2001).

Results of our study do not support these assumptions, since we did not find correlations between the level of corticothalamic coupling and secondary generalization or seizure duration. In contrast, the existence of an early loss of consciousness was found to be correlated with the extent of mesial–lateral network involvement and of thalamocortical interactions. The fact that early loss of consciousness is related to mesial–lateral involvement is in agreement with a previous clinical study (Maillard *et al.*, 2004). The correlation with thalamocortical coupling suggests that seizures affecting the thalamic region could alter the sensory information process passing through the thalamus early. Results are in agreement with a recent metabolic study correlating cerebral blood flow (CBF) during temporal lobe seizures and the alteration of consciousness (Blumenfeld *et al.*, 2004). Authors found that temporal lobe seizures associated with loss of consciousness produced CBF increases in the temporal lobe, followed by increases in bilateral midline subcortical structures. In contrast, temporal lobe seizures in which consciousness was spared were not accompanied by these widespread CBF changes.

Relation with the surgical prognosis

TLE surgery has benefited from several important advances during the past two decades. Results however vary considerably between epilepsy surgery centres with rates of Engel class I outcome ranging from 33 to 93% among recent published series (McIntosh *et al.*, 2001). Failure of temporal lobe surgery remains an important and debated issue. The main factor contributing to these failures is probably the incomplete resection of the epileptogenic zone. For example, an insufficient resection of the mesial temporal structures is associated with a higher risk for seizure recurrence (Hennessy *et al.*, 2000).

Another putative cause of epilepsy surgery failure is that patients might suffer from a complex epileptogenic network, including a combination of brain regions located within the temporal lobe and over the closed neighbouring structures. The patients included in this study had anterior temporal lobectomy, or, in two, a cortectomy limited to the neocortex (superior temporal gyrus) in cases of lateral TLE.

Despite its limitation due to the low number of patients, our study suggests that the post-surgical prognosis could be related to the extension of the epileptogenic network to the subcortical (here, thalamic) structures. Indeed, we found that the post-surgical results were better when low values of thalamocortical synchrony were found and worse in case of high index of thalamocortical synchrony.

This suggests that classical surgery aiming at removing the cortical temporal lobe structures may be insufficient in some cases to disrupt all the involved networks. This could be an additional explanation of the failure of classical anterior temporal lobectomy in patients with TLE seizures.

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