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Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal 'plus' epilepsies

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Temporal 'plus' epilepsies are characterized by seizures involving a complex epileptogenic network including the temporal lobe and the closed neighboured structures such as the orbito-frontal cortex, the insula, the frontal and parietal operculum and the temporo–parieto–occipital junction. Temporal 'plus' epilepsies are currently identified by means of intracerebral electrodes but whether their diagnosis can be suspected non-invasively has not been evaluated yet. The aim of this retrospective study was to address this issue in 80 consecutive patients who were thought to suffer from non-lesional temporal lobe seizures which finally proved, on the basis of stereotactic intracerebral EEG (SEEG) recordings, to be 'purely' temporal (TL group, $n = 58$) or temporal 'plus' (T+ group, $n = 22$). Our results showed that the two groups of patients were difficult to differentiate on the basis of general clinical features or MRI data. Even the presence of hippocampal sclerosis did not distinguish the two groups. Conversely, both ictal clinical symptoms and scalp-EEG findings significantly differentiated TL from T+ patients. Patients with TL epilepsies more frequently presented an ability to warn at seizure onset ($P = 0.003$), an abdominal aura ($P = 0.05$), gestural automatisms ($P = 0.04$) and a post-ictal amnesia ($P = 0.02$). Patients suffering from T+ epilepsies more frequently had gustatory hallucinations ($P = 0.02$), rotatory vertigo ($P = 0.02$) and auditory illusions ($P = 0.02$) at seizure onset; they exhibited more frequently contraversive manifestations of the eyes and/or head ($P = 0.001$), piloerection ($P = 0.03$) and ipsilateral tonic motor signs ($P = 0.05$), and they were more often dysphoric in the post-ictal phase ($P = 0.0001$). Cluster analysis mainly indicated that some associations of symptoms were relevant for differentiating TL cases from T+ cases. Interictal EEG of T+ patients more frequently exhibited bilateral or precentral abnormalities, while ictal EEG more frequently pointed over the anterior frontal, temporo-parietal and precentral regions. Neither TL interictal spikes, nor TL ictal EEG onset, allowed us definitely to rule out the possibility of T+ epilepsies. Our findings may be useful for identifying, among patients suffering from 'atypical' non-lesional TL epilepsies, those who should undergo invasive recordings before surgery.

Keywords: temporal plus epilepsies; temporal lobe epilepsies; intracerebral EEG; epilepsy surgery

Abbreviations: SEEG = stereotactic intracerebral EEG; TF = temporo-frontal; TS = temporo-sylvian

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Introduction

The term of temporal 'plus' (T+) epilepsies has recently been suggested (Ryvlin and Kahane, 2005) to describe specific forms of seizures of multilobar origin which are characterized by the involvement of a complex epileptogenic network including the temporal lobe and the closed neighboured structures, such as the orbito-frontal cortex, the insula, the frontal and parietal operculum and the temporo–parieto–occipital junction. There are, however, very few published data on this topic (Munari *et al.*, 1980; Kahane *et al.*, 2001), thus making the identification of this form of epilepsy largely ignored. Yet, some patients submitted to temporal lobe surgery who continue to experience seizures postoperatively, might suffer from T+ epilepsies, and identifying those patients by means of invasive recordings, might lead to performing a more extensive and effective cortectomy, according to surgical possibilities and limits (Munari *et al.*, 1995). In a depth EEG study aiming at verifying the role of the perisylvian cortex in seizures involving the temporal lobe, Kahane *et al.* (2001) showed that six of the seven patients in whom seizures arose from temporal and suprasylvian opercular

cortices, and in whom an adequate temporo-perisylvian resection could be achieved, were totally seizure-free after surgery. In contrast, temporal lobe surgery alone was unsuccessful in the two temporo-insular cases of Isnard *et al.* (2004), since it allowed them to suppress the seizures of temporal lobe origin, but not those which arose from the insula. Moreover, anterior temporal resection did not benefit the patients with ictal temporo-parietal symptoms (reported by Aghakhani *et al.*, 2004), and temporal lobectomy failed to control seizures in four of the six patients with posterior basal temporal ictal onset, reported by Prasad *et al.* (2003). These examples, though limited, emphasize how important it is to delineate the spectrum of T+ epilepsies better, as patients suffering from this form of epilepsy might be at higher risk of sudden death than those suffering from « pure » temporal lobe epilepsies (Persson *et al.*, 2005).

We therefore performed a retrospective study in 80 consecutive patients who, we suspected were suffering from non-lesional temporal lobe epilepsy and in whom, on the basis of stereotactic intracerebral EEG (SEEG) recordings, the epileptogenic zone was defined as temporal (TL) or temporal plus (T+). The main aim of this study was to identify clinical features of seizures that eventually allowed to distinguish these two groups of patients, apart from SEEG findings. Whether general clinical features, MRI data and scalp-EEG recordings were helpful for differentiating the two groups was also evaluated.

Patients and methods

The 80 patients included in this retrospective study, were part of a group of 212 consecutive patients suffering from medically intractable seizures and who were operated on, after SEEG recordings, at Grenoble Hospital from 1990 to 1998. They were selected on the basis of the following criteria: (i) absence of any detectable lesion on MRI, with the exception of hippocampal sclerosis; (ii) SEEG recordings showing that seizures involved at least mesial and/or lateral TL structures; (iii) surgery performed according to SEEG results, taking into account anatomical constraints and (iv) at least 5 years of post-operative follow-up.

Patients

They were 42 females and 38 males, whose mean age at SEEG recordings was 29.3 ± 8.7 years. Medical history of the patients showed that mean age at epilepsy onset was 10.1 ± 7.9 years, and mean duration of epilepsy was 19 ± 8 years. Thirty-seven patients (46%) experienced febrile seizures in childhood. Seizures frequency ranged from 1 to 150 per month (mean: 13.5 ± 17.5 per month). The possible occurrence of seizures during sleep was found in 31 patients (39%), and occasional secondary tonic–clonic generalization was reported in 18 patients (22%). Sixty-six patients (82.5%) had a unilateral hippocampal sclerosis, always ipsilateral to the epileptogenic region. The remaining 14 patients (17.5%) showed no clear MRI abnormalities prior to surgery. In two of these last patients, however, neuropathology examination revealed a hamartoma in one, and a non-Taylor type cortical dysplasia in the other.

Presurgical evaluation and surgery

First, all patients underwent long-term scalp video-EEG monitoring (Biomedical Monitoring System, Campbell, USA; since 1996: Micromed, Treviso, Italy). The international 10–20 electrode system was used in all cases, with additional temporal basal electrodes (F9/10, T9/10) in many patients. No other electrodes (nasopharyngeal, sphenoïdal, foramen ovale, . . .) were utilized. In 79 of the 80 patients, 1 to 29 seizures were recorded (total number: 432), all involving at least the temporal lobe. A SEEG study, however, was judged necessary because electroclinical arguments suggested either a possible lateral temporal or extratemporal seizure onset, or an early spread of seizures outside the temporal lobe (i.e. involving other electrodes than F7/8, T3/4, T5/6 and, when present, F9/10, T9/10). In the remaining patient, seizures were not captured during the video-EEG monitoring, but interictal abnormalities, as well as the direct visualization of an ictal episode by the medical staff, were judged sufficient to decide to perform a SEEG.

Then, the 80 patients were evaluated by a total number of 888 chronically stereotactically implanted intracerebral electrodes, according to the SEEG methodology developed by Bancaud and Talairach (1973). Seven to fifteen multilead electrodes (Dixi, Besançon, France) were implanted per patient, in temporal and extratemporal areas depending on the suspected origin and region of early spreading of seizures (Munari *et al.*, 1994). Video–SEEG recordings were conducted extra-operatively in chronic conditions with reduced medication. The same audio-video-EEG monitoring system as for scalp-EEG monitoring was used, which allowed to record simultaneously up to 128 depth EEG channels. A total number of 607 seizures were recorded in 79 of the 80 patients (1 to 44/patient). In the remaining case, who had a hippocampal sclerosis, the SEEG study was prematurely interrupted due to a venous thrombosis of the legs. Therefore, seizures could not be recorded, but interictal abnormalities were informative enough for us to decide to perform an antero-mesial temporal lobectomy, and the patient was cured after surgery.

Based on SEEG findings, the epileptogenic zone was lateralized in the right hemisphere in 56 cases (70%), and in the left hemisphere in 24 cases (30%). The term of « epileptogenic zone » referred to the amount of cortex that was considered to be removed to render the patient seizure-free. Particular attention was paid to first clear ictal SEEG change, which was considered as relevant only when it occurred prior to the clinical onset of the seizure, and when it manifested by a fast synchronizing discharge (low-voltage fast activity or recruiting fast discharge of spikes). The epileptogenic zone was therefore defined as temporal in 58 patients (TL Group), and temporal 'plus' in 22 patients (T+ Group) due to the fact that, in this latter group, it included not only mesial and lateral temporal lobe structures, but also the inferior frontal cortex [temporo-frontal (TF) group, $n = 9$], the supra-sylvian opercular cortex [temporo-sylvian (TS) group, $n = 7$] or the temporo–parieto–occipital junction (TPO group, $n = 6$).

In all 80 cases, surgery consisted of a tailored resection which included at least the temporal pole and mesio-temporal lobe structures (amygdala, hippocampus and para-hippocampal gyrus). The posterior limits of the temporal neocortical resection varied according to SEEG results (Fig. 1A). Additionally, in 18 of the 22 T+ patients, surgery was extended outside the temporal lobe,

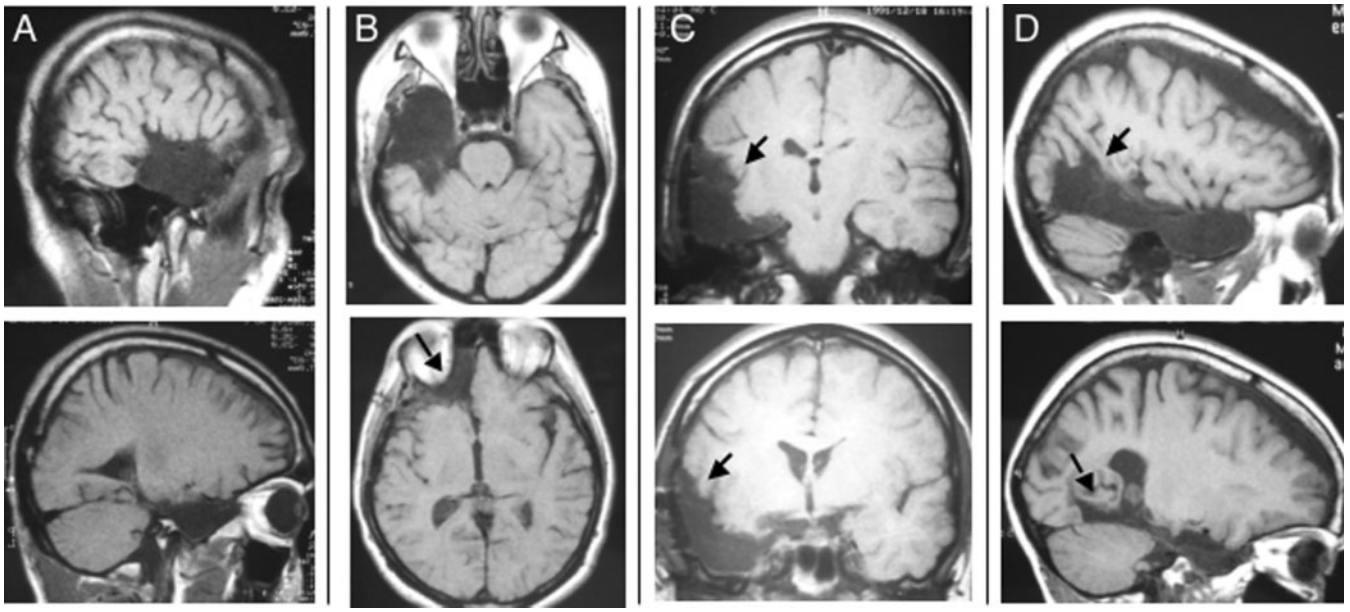

Fig. 1 Examples of resections. (**A**) Right TL cryptogenic case. Complete right temporal lobectomy. (BCD) T+ cases. (**B**) Right temporo-frontal epilepsy with hippocampal sclerosis. TL resection + ipsilateral orbitofrontal resection (arrow). (**C**) Right temporo-sylvian epilepsy with hippocampal sclerosis. TL resection + fronto-central opercular resection (arrows). (**D**) R T+ posterior epilepsy with hippocampal sclerosis. TL resection + mesio-lateral temporo-occipital resection (arrows).

including the orbito-frontal cortex ($n = 6$) (Fig. 1B), the frontal pole and orbito-frontal cortex ($n = 1$), the postero-inferior dorsolateral prefrontal cortex ($n = 1$), the parietal operculum ($n = 2$), the central and parietal opercula ($n = 4$) (Fig. 1C), the inferior parietal cortex ($n = 1$) and the basal or basal–lateral temporo–occipital junction ($n = 3$) (Fig. 1D). Because of functional anatomical constraints, the cortectomy could not include the whole epileptogenic area in 4 of the 22 T+ patients in whom seizures arose from the dominant hemisphere and involved Broca's area ($n = 1$) or Wernicke's area ($n = 3$).

Post-operative seizure status, according to Engel's classification (Engel *et al.*, 1993), showed that 51 TL patients were in class I (88%) and 7 in class II, whereas 16 T+ patients were in class I (73%), 3 in class II, 1 in class III and 2 in class IV.

Data analysis

General clinical and MRI features

The two groups of patients (TL and T+) were compared using ANOVA tests for age at seizure onset, age at SEEG, epilepsy duration and seizure frequency, and using Phi and Cramer V tests for sex ratio, seizure lateralization and duration, presence/absence of secondary tonic–clonic generalization and presence/absence of seizures during sleep. Presence of mesio-temporal sclerosis and febrile seizures was computed by means of contingency tables.

Scalp-EEG findings

EEG data were analysed using a bipolar representation. Interictal abnormalities were classified according to their type (spikes, slow waves, both), their lateralization (right, left, bilateral) and their localization (according to the 10–20 system). Seizure onset was lateralized and localized similarly. Ictal EEG onset was defined by the occurrence of a low-voltage fast (beta) activity, by the occurrence of a well-localized flattening, by the disappearance of well-localized interictal EEG abnormalities, or (in the absence of the three previous patterns) by the occurrence of a rythmic theta activity. Contingency tables were computed in order to compare TL and T+ groups, both for interictal and ictal EEG data.

Clinical seizure analysis

Ictal clinical symptoms were assessed during SEEG-recorded seizures in all but one patient. This allowed us, notably, to exactly evaluate the seizure duration which was calculated from the SEEG onset of the seizure to its SEEG end. In the only patient in whom seizures were not recorded during SEEG, we considered only the typical seizure recorded during video-EEG monitoring, and seizure duration was evaluated on the basis of clinical features. All the 607 SEEG-recorded seizures were reviewed but, in order to avoid biasing our quantitative analysis (the number of seizures per patient ranged from 1 to 44), we analysed only one seizure per patient. We decided to analyse the first seizure(s) clearly recognized by the patient or the patient's family as typical of the patient's epilepsy, and in which we could identify the commonest clinical signs reported. We checked that these signs were consistent with those observed during the other typical seizures (when they existed), as well as with those observed during scalp video-EEG monitoring. We did not take into account seizures in

which only auras occurred, or seizures which ended by unusual secondary generalization. Finally, we included in the analysis subjective symptoms described as very common in the recent history of the patients, even when their occurrence was just reported at the very beginning of seizures, without a complete description, due to the fact that the patient was eventually amnesic of his/her aura.

Seizure semiology was analysed according to a working definition of ictal and post-ictal symptoms (Table 2). First, the relative frequency of symptoms was calculated for TL Group and T+ Group. Then, contingency tables were computed between the TL and T+ groups for all clinical events. Since we dealt with nominal variables (i.e. TL or T+ epilepsies, and presence or absence of the event), we used the Phi and Cramer V coefficients to evaluate contingency tables significance, which was then set at $P \leq 0.05$. For symptoms which were significantly more frequent in T+ group than in TL group, we performed the following additional analysis: (i) comparison between the three T+ subgroups (TF, TS, TPO) in order to assess with which subgroup those symptoms were significantly associated; (ii) contingency tables between each of the T+ subgroups and the TL group, in order to detect which of the T+ subgroups significantly differed from the TL group. Finally, we carried out a cluster analysis of the ictal and post-ictal symptoms to evaluate which type of events appeared together more frequently in our patients. Ex-post information about the diagnostic group of subjects (TL and T+) was not included. Cluster analysis measures similarity between events: initially each event is considered to be a cluster; subsequently, the most similar clusters are joined to form a new cluster, until a single cluster is obtained that contains all events. The criterion used to combine events is called the 'amalgamation rule' (Kotagal *et al.*, 1995). As the amalgamation rule, the average linkage (an average measure of similarity to form clusters) was applied, while, to measure the degree of association between two events, the correlation coefficient Phi was used, suitable for binary variables. In order to have a manageable number of clusters, we set a cut-off at 30 clusters starting from the 72 non-zero events, since with this number of clusters the value of the intra-cluster correlation coefficient resulted always greater than 0.2 and could be considered significant ($P \leq 0.05$); nevertheless, cluster analysis is a descriptive statistical tool, and there are not well-established methods to a-priori define the number of clusters, but case-to-case decisions depending on the data under analysis. Having obtained the clusters, we examined the composition of the events, referring to the previously computed contingency tables, in order to determine how many specific events from a given cluster were significantly more frequently present in the T+ group with respect to the TL group. Furthermore, for events more frequently found in the T+ group, we assessed with which of the T+ subgroups each event might be significantly associated.

Results

General clinical and MRI features (Table 1)

There was no statistical difference between TL group and T+ group when comparing sex ratio, age at SEEG, age at onset of epilepsy, past history of febrile seizures, epilepsy duration, seizure frequency and seizure duration, presence of seizures during sleep and occasional secondary tonic–clonic generalizations, and presence of mesio-temporal sclerosis on MRI. In particular, febrile seizures were experienced by 27 of the 58 TL patients (46.6%), and by 10 of the 22 T+ patients (45.5%) and the difference was non-significant. The only significant difference between the two groups concerned the left-side predominance of seizures in TL patients ($P < 0.0001$), a finding which possibly reflects a selection bias. Indeed, were included in the study only those patients submitted to surgery, after SEEG evaluation. Patients in whom ictal scalp-EEG recordings clearly demonstrated without ambiguity an initial involvement of eloquent cortical areas (i.e. initial ictal aphasia) were usually not considered for further evaluation. Additionally, a significant number of patients who were suffering from T+ epilepsies and whose epileptogenic zone

Table 1 General clinical, MRI and scalp-EEG features in patients suffering from temporal lobe epilepsies (TL group, $n = 58$) and in patients suffering from temporal 'plus' epilepsies (T+ group, $n = 22$). The only significant difference between the two groups concerned the left-side predominance of seizures in TL patients ($P < 0.0001$) (see 'Results' section for explanation). Regarding scalp-EEG features, interictally, T+ patients more frequently exhibited bilateral and precentral spikes and/or slow waves, while ictally, the first EEG changes were more frequently localized over the anterior frontal, the temporo-parietal and/or the precentral regions. pt: number of patients; * age and disease duration at surgery; HS: hippocampal sclerosis.

	Temp	Temp+	p
General and MRI features			
Sex	27 M	11 M	NS
Age at seizure onset	9.68 ± 7.83	11.39 ± 8.06	NS
Age*	29.07 ± 7.01	29.86 ± 12.40	NS
Febrile seizures	27pt	10pt	NS
Disease duration*	19.3 ± 7.55	18.39 ± 9.43	NS
Seizure frequency per month	14.36 ± 20.05	11.4 ± 7.8	NS
Tonic-clonic generalizations	16 pt	2 pt	NS
Nocturnal seizures	22 pt	9 pt	NS
Lateralization	4 L	20 L	<0.0001
HS (MRI and/or histology)	49	17	NS
EEG features			
Bilateral spikes and/or slow waves	8.5%	43.5%	<0.0001
Precentral spikes and/or slow waves	1.7%	43.5%	<0.0001
Fronto-anterior seizure onset	0%	8.70%	0.02
Temporo-parietal seizure onset	8.5%	26.1%	0.04
Precentral seizure onset	0%	21.7%	<0.0001

proved to include eloquent cortical areas after SEEG evaluation were not operated on. This represented eight patients during the 1990–98 period, in whom T+ seizures arised from the left hemisphere in six (TO : 3, TPO : 2, TF : 1), and from the right hemisphere in two (TP : 1, TF : 1).

Scalp-EEG findings (Table 1)

The statistically significant differences found between the TL group and the T+ group were the following:

a) interictally, T+ patients more frequently exhibited bilateral spikes and/or slow waves, as well as precentral (F4-C4; F3-C3) spike-and-waves complexes;
b) ictally, the first EEG changes were more frequently localized over the anterior frontal (FP2-F4; FP1-F3) region, the temporo-parietal (T5-P3; T6-P4) region and the precentral (F4-C4; F3-C3) region in the T+ group than in the TL group. These changes, when comparing each of the T+ subgroups with the TL group, were found to be more frequently associated with the TF subgroup, the TPO subgroup and the TS subgroup, respectively.

Seizure clinical semiology (Tables 2 and 3)

We analysed 80 seizures in the 80 patients (1 per patient): 58 in the TL group, and 22 in the T+ group (9 TF, 7 TS, 6 TPO).

Altogether, auras of varying types were experienced in most of the seizures (71/80, 88.7%), and they were mainly characterized by digestive symptoms (71%). Consciousness was impaired in all but three seizures. Autonomic changes were frequently observed, and most often consisted of cardiovascular signs (60%). Both simple motor signs and complex behaviours were seen in the majority of cases. The former most often consisted of tonic motor signs (48.7%) and versive manifestations (43.7%), whereas the latter mainly consisted of oroalimentary (75%) and gestural automatisms (67.5%). Post-ictal confusion was common (45%) and patients were very frequently amnesic of the ictal phase (76.2%), although the aura was usually remembered.

Overall, the statistically significant differences in clinical behaviour between the two groups were as follows (Table 2). Patients with TL epilepsies more frequently presented an ability to warn at seizure onset ($P = 0.003$), a digestive aura ($P = 0.02$), gestural automatisms ($P = 0.04$), and a post-ictal amnesia ($P = 0.02$). The only type of digestive aura which was associated with TL epilepsies consisted of abdominal aura ($P = 0.05$). Patients suffering from T+ epilepsies more frequently had gustatory hallucinations ($P = 0.02$) and vestibular illusions ($P = 0.03$) at seizure onset, they more frequently exhibited versive manifestations of the eyes and/or head ($P = 0.04$), and they were more often dysphoric in the post-ictal phase ($P = 0.0001$). When analysing this clinical symptomatology in more detail, it appears that the differences observed for vestibular symptoms and oculocephalic signs more especially concerned rotatory vertigo ($P = 0.02$) and contralateral version of the head and/or eyes ($P = 0.001$), respectively. Also, although auditory symptoms, thermoregulatory changes, and tonic motor signs considered as a whole, did not allow us to distinguish the two groups of patients, a statistically significant association with T+ epilepsies was found for auditory illusions ($P = 0.02$), piloerection ($P = 0.03$) and ipsilateral tonic motor signs ($P = 0.05$). Among T+ cases, the only statistically significant associations with respect to subgroups were found for gustatory auras and the TS subgroup ($P = 0.009$), and for vestibular auras and the TPO subgroup ($P = 0.02$).

Cluster analysis allowed us to obtain 30 clusters. When analysing the event composition of these clusters, we found that five clusters comprised at least one event showing a statistically significant association either with the TL group (TL clusters) or with the T+ group (T+ clusters) (Table 3). The two TL clusters (clusters 13 and 28) included one cluster which was composed of different kinds of digestive auras (cluster 13), and one cluster which was composed of post-ictal amnesia and chewing automatisms (cluster 28). These two TL clusters were composed of events that were all found more frequently in the TL group. The three T+ clusters comprised at least one event which showed a statistically significant association with the T+ group (clusters N°2, 3 and 9). The other events constituting these three T+ clusters were also found more frequently in the T+ group than in the TL group, although the difference did not reach significance. Two of these three T+ clusters (clusters 2 and 3) were composed of events which were all found more frequently in the TPO subgroup. One was composed only of auditory symptoms (cluster 3), while the other comprised many events including different types of auras (emotional, psychic, visual and vestibular) and different types of simple motor signs (tonic and giratory) (cluster 2). We did not find any preponderance for one of the T+ subgroups in the last T+ cluster (cluster 9), which consisted of anxiety and contraversive manifestations.

Discussion

Though the existence of T+ epilepsies has long been demonstrated by SEEG recordings, and confirmed by our daily practice, data on this topic remain serendipitous (Munari *et al.*, 1980, 1995; Kahane *et al.*, 2001). Particularly, whether the diagnosis of T+ epilepsy can be suspected non-invasively, has not been evaluated. The aim of the present study was to address this issue in two groups of epileptic patients whose seizures, on the basis of SEEG recordings, were defined as temporal (TL group) or temporal 'plus' (T+ group), paying particular attention to ictal clinical symptomatology.

Table 2 Ictal and post-ictal clinical signs in temporal lobe seizures (TL group, $n = 58$) and temporal 'plus' seizures (T+ group, $n = 22$)

Symptoms main categories	Subcategories	Relative frequency of ictal events(%) TL group	T+ group	*P*
seizure duration (>1 min)		78	73.9	0.7
consciousness impairement ability		94.9	100	0.27
to warn at seizure onset aura #		**78**	43.5	**0.003**
none		15.3	8.7	0.4
somatosensory	(Ipsilateral/contralateral/bilateral)	16.9 (11.9/15.3/11.9)	26.1 (8.7/26.1/26.1)	0.3 (ns/ns/ns)
visual	(Illusions/hallucinations)	6.8 (5.1/1.7)	13 (13/4.3)	0.36 (0.02/ns)
auditory	(Illusions/hallucinations)	3.4 (0/3.4)	8.7 (8.7/4.3)	0.32 (ns/ns)
olfactory	(Hallucinations)	1.7	4.3	0.48
gustatory	(Hallucinations)	5.1	**21.7**	**0.02**
vestibular	(Rotatory/not rotatory)	1.7 (0/1.7)	**13** (**8.7**/4.3)	**0.03** (**0.02**/ns)
dysmnesic	(Familiarity illusion/memory flashback/dreamy state)	5.1 (0/3.4/1.7)	13 (0/8.7/4.3)	0.2 (ns/ns/ns)
emotional	(Fear/anxiety/anger/pleasure)	33.9 (22/11.9/3.4/0)	39.1 (13/21.7/4.3/0)	0.6 (ns/ns/ns/ns)
other psychic	(Forced thinking/distorsion of reality/urge to move)	3.4 (0/3.4/0)	4.3 (0/4.3/0)	0.8
cephalic		6.8	4.3	0.8
digestive	(Throat/chest/abdomen)	**71.2** (16.9/54.2/**6.8**)	43.5 (13/30.4/4.3)	**0.02** (ns/ns/0.05)
uro-genital		1.7	4.3	0.48
staring		32.2	43.5	0.34
looking around		32.2	39.1	0.5
autonomic changes				
cardiovascular	(Tachycardia/bradycardia/pallor or flushing)	61 (27.1/0/15.3)	52.2 (26.1/0/13)	0.46 (ns/ns/ns/ns)
respiratory	(Apnoea/bradypnoea/polypnoea/cough)	28.8 (10.2/1.7/15.3/3.4)	17.4 (4.3/0/8.7/0)	0.29 (ns/ns/ns/ns
thermoregulatory	(Sensation of heat or cold/sweat/ pilo-erection)	20.3 (15.3/3.4/1.7)	30.4 (13/4.3/**13**)	0.33 (ns/ns/0.03)
pupillary changes *		16.9	26.1	0.35
vomiting		0	0	0.73
sialorrhea		25.4	21.7	
urination		0	0	
simple motor signs $				
dystonic posturing	(Ipsilateral/contralateral/bilateral)	30.5 (3.4/27.1/0)	21.7 (4.3/17.4/0)	0.43 (ns/ns/ns)
tonic motor	(Ipsilateral/contralateral/bilateral)	37.3 (25.4/37.3/25.4)	60.9 (**47.8**/52.2/39.1)	0.13 (0.05/ns/ns)
clonic motor	(Ipsilateral/contralateral/bilateral)	33.9 (18.6/25.4/20.3)	21.7 (21.7/13/13)	0.28 (ns/ns/ns)
version (head and/or eyes)	(Ipsilateral/contralateral/bilateral)	35.6 (32.2/10.2/0)	**60.9** (30.4/**43.5**/0)	**0.04** (ns/**0.001**/ns)
giratory	(Ipsilateral/contralateral/bilateral)	3.4 (3.4/0/0)	13 (8.7/4.3/0)	0.1 (ns/ns/ns)
complex behaviours @				
oroalimentary automatisms	(Chewing/swallowing)	76.3 (59.3/27.1)	65.2 (56.5/13)	0.3 (ns/ns)
gestural automatisms	(Ipsilateral/contralateral/bilateral)	**67.8** (43.5/34.8/34.8)	43.5 (57.6/37.3/27.1)	0.04 (ns/ns/ns)
nose rubbing		5 1	4 3	0.8
verbal automatisms		20.3	13	0.4
laughing or crying		8.5	4.3	0.5
moaning		16.9	26.1	0.35
hypermotor behaviours		30.5	43.5	0.26
postictal signs				
confusion		40.7	52.2	0.35
motor deficit		11.9	4.3	0.3
language deficit		42.4	39.1	0.78
automatisms		42.4	47.8	0.65
dysphoric state **		6.8	**39.1**	**0.0001**
amnesia		**81.4**	56.5	**0.02**

Note: More than one sign or behaviour of the same category could coexist in the same individual. (#) Auras were subjective sensations, the description of which was obtained at the time they occurred, during the post-ictal interview, or on the basis of the recent history of the patients. ($) Simple (or elementary) motor signs were defined as a 'single type of contraction of a muscle or a group of muscles that is usually stereotyped and not decomposable into phases' (Blume *et al*., 2001); they could involve the head, the face and/or body segments, and they were differentiated in 'tonic' motor signs (which are sudden movements of the type that can, for instance, be elicited by the electrical stimulation of the premotor and motor cortices, see Chauvel *et al*., 1992) and 'dystonic' motor signs (which are sustained unnatural posturing of one upper extremity with rotational component, and are classically associated with TL seizures, see Kotagal *et al*., 1995). (@) Complex behaviours looked like natural behaviours; gestural automatisms essentially affected the distal body segments and they were characterized by 'more or less coordinated, repetitive, motor activity that often resembles a voluntary movement and may consist of an inappropriate continuation of ongoing pre-ictal motor activity' (Blume *et al*., 2001); hypermotor behaviours were much more proximal and violent, and often appeared as reactions to a marked affective state. (*) Mydriasis or myosis. (**) Depression or euphoria. Contingency tables significance was set at $P \leq 0.05$; ns: not significant. The significant values are in bold.

Table 3 Cluster analysis

Cluster number	Event	Frequency (%)		
		TL group	T+ group	*P*
2	Rotatory vertigo	0	8.7	0.02
2	Visual illusions	5.1	13	NS
2	Visual hallucinations	1.7	4.3	NS
2	Anger	3.4	4.3	NS
2	Distorsion of reality	3.4	4.3	NS
2	Ipsilateral tonic motor signs	25.4	47.8	0.05
2	Contralateral giration	0	4.3	NS
2	Bilateral tonic motor signs	25.4	39.1	NS
2	Contralateral tonic motor signs	37.3	52.2	NS
3	Auditory hallucinations	3.4	4.3	NS
3	Auditory illusions	0	8.7	0.02
9	Anxiety	11.9	21.7	NS
9	Contralateral versive manifestations	10.2	43.5	0.001
13	Abdominal aura	54.2	30.4	0.05
13	Pharyngeal aura	16.9	13	NS
28	Post-ictal amnesia	81.4	56.5	0.02
28	Chewing automatisms	59.3	56.5	NS

Note: Two clusters comprised at least one event which showed a statistically significant association with the TL group (clusters 13 and 28) and three clusters comprised at least one event which showed a statistically significant association with the T+ group (clusters 2, 3 and 9). Clusters 2 and 3 showed a statistically significant association to TPO subgroup.

Our results, although not conclusive, showed that the two groups of patients were difficult to distinguish on the basis of general clinical features or MRI data. A history of frequent secondary tonic–clonic generalization, which has been proved recently to have bad post-operative prognostic significance after temporal lobectomy (McIntosh *et al.*, 2004; Jeong *et al.*, 2005), did not allow us to discriminate between the two groups. Furthermore, the presence of hippocampal sclerosis, which is known as one of the best prognosis factors for successful temporal lobe surgery (Garcia *et al.*, 1994; Arruda *et al.*, 1996; Berkovic *et al.*, 1996), did not distinguish TL from T+ patients. Conversely, both ictal clinical symptoms and scalp-EEG findings significantly differentiated TL and T+ patients as discussed in the following paragraphs.

Obviously, a limitation linked to intracerebral EEG recordings is that most of the brain volume remains unexplored. Therefore, we cannot definitively rule out that the identification of our groups of patients may be in part erroneous, notably regarding the T+ subgroups. This risk, however, appears low since the number of electrodes used per patient was relatively high (11 in average, resulting in more than 100 recording sites), their placement allowed in all cases to evaluate temporal and extratemporal areas, and electrodes were positioned to target-specific functional systems so that the spatial sampling precision was much higher within such systems (Kahane *et al.*, 2004).

Auras

Digestive symptoms—and particularly epigastric sensations—were very commonly showed by both TL and T+ patients. An epigastric aura, however, appeared more frequently at seizure onset in the TL group than in the T+ group, and the difference was statistically significant. Cluster analysis confirmed this finding, showing also that the coexistence of different kind of digestive auras (i.e. abdominal and pharyngeal) might be an indicator of a TL onset of the seizures (cluster 13, Table 3). These results are coherent with previous reports about abdominal aura being more common in TL seizures than in other seizure types (Henkel *et al.*, 2002), especially in the context of mesio-temporal lobe epilepsy with hippocampal sclerosis (Wieser *et al.*, 2004).

Conversely, gustatory, vestibular and auditory symptoms, the localizing significance of which remains uncertain (Hausser-Hauw and Bancaud, 1987; Cascino and Karnes, 1990; Salanova *et al.*, 1995; Manford *et al.*, 1996; Kluge *et al.*, 2000; Maillard *et al.*, 2004; Wiest *et al.*, 2004; Rossetti *et al.*, 2005), were found more frequently associated with T+ epilepsies. Our data even suggested that gustatory and vestibular auras might help to differentiate the T+ subgroups. Gustatory hallucinations, indeed, were more specifically associated with the TS subgroup, i.e. the group of patients whose seizures involved TL structures and the insulo-opercular cortex at onset. This result is coherent with cortical electrical stimulation studies, showing that the suprasylvian opercular cortex and/or the insula might play an important role for the occurrence of gustatory symptoms (Hauser-Hauw and Bancaud, 1987; Ostrowsky *et al.*, 2000; Isnard *et al.*, 2004). It is also in agreement with the superior insula and frontoparietal representation of taste suggested by functional neuroimaging techniques (Small *et al.*, 1999), as well as with the specific insular responses to disgust observed during neurophysiological and fMRI experiments (Krolak-Salmon *et al.*, 2003; Wright *et al.*, 2004). Vestibular illusions of rotation, by comparison, were more particularly associated with T+ epilepsies involving the TPO junction. This result is coherent with our cluster analysis which showed that vestibular illusions, when part of a complex visual-emotional-dysmnesic experience associated with different kinds of simple motor signs, also pointed to a possible TPO seizure onset (cluster 2, Table 3). It is also in line with a recent case report of a patient who suffered from an epileptic rotatory vertigo arising from the TPO junction (Altay *et al.*, 2005), and with a cortical electrical stimulation study we performed a few years ago, where we identified a lateral cortical temporoparietal area from where rotatory sensations were particularly easily elicited (Kahane *et al.*, 2003). Auditory signs did not allow differentiation between the T+ subgroups, although cluster analysis suggested that the association of auditory hallucinations and illusions might be an indicator of TPO seizures (cluster 3, Table 3).

The distinction between T+ epilepsies and TL epilepsies concerned only auditory illusions, a puzzling finding which suggests that an auditory aura might have different localizing significance depending on its type. This hypothesis is somehow in accordance with Bancaud's assumption that auditory illusions occur preferentially when epileptic discharges are widely extended over the superior temporal gyrus, while auditory hallucinations are likely to occur when discharges are more limited in space (Bancaud, 1987). It also confirmed, as suggested by others (Clarke *et al.*, 2003; Aghakhani *et al.*, 2004), that in the context of TL epilepsies, patients with auditory auras may have an extensive epileptogenic zone out-passing the limits of the temporal lobe.

Ability to warn at seizure onset

The capacity to advise of seizure occurrence depends both on the preservation of speech capacities and of consciousness when the patient is experiencing an aura. This capacity was more impaired in T+ patients than in TL patients, although auras occurred with the same frequency in both groups. It is unlikely that this difference was due to language deficits, since these were expected to occur more frequently in the TL group, which showed a significantly higher left-side lateralization of seizures. Alternatively, the fact that T+ epilepsies initially involved a large amount of cortex, including temporal and juxta-temporal areas, could explain why consciousness impairment occurred earlier in T+ patients than in TL patients. Indeed, previous findings suggested that loss of contact in TL epilepsies is the consequence of the extent of the discharge out of the temporal lobe (Munari *et al.*, 1980).

Autonomic symptoms

Although many autonomic signs were studied, the only significant difference detected between the two groups concerned the occurrence of piloerection, a symptom which was found more frequently in T+ epilepsies. That is a rare epileptic manifestation which occur predominantly in patients with TL seizures, although many other localizations have been found, in frontal, fronto-parietal, fronto-temporal, parieto-occipital and insular cortices (Fish *et al.*, 1993; Freeman and Schachter, 1995; Seek *et al.*, 2003; Seo *et al.*, 2003; Loddenkemper *et al.*, 2004; Usui *et al.*, 2005). In fact, generator(s) of epileptic piloerection seem to be located in close vicinity to structures which are part of the central autonomic network (Benarroch, 1993), and the significant correlation we found between piloerection and T+ epilepsies might be due to a more extended involvement of this network at seizure onset. Whether the insula, as suggested by some authors (Lesser *et al.*, 1985; Warren, 2002; Loddenkemper *et al.*, 2004), plays a pivotal role in the genesis of this sign remains a debatable issue.

Motor signs

Elementary motor signs as well as complex behaviours were commonly found in TL and T+ patients. However, we found a significant association of gestural automatisms with TL epilepsies, a finding which is in accordance with literature data (Kotagal *et al.*, 2003). This might be due to the predominant involvement of mesio-temporal lobe structures during TL seizures, while during T+ seizures—which often largely involve the temporal neocortex together with juxta-temporal areas—mesio-temporal lobe structures are not necessarily implicated. This hypothesis, though debatable, is supported on the one hand by the more frequent observation of gestural automatisms during mesio-temporal lobe seizures than during neocortical or mesio-lateral temporal lobe seizures (Maillard *et al.*, 2004), and on the other hand by the especially high rate of gestural automatisms in TL seizures associated with medio-temporal lobe lesions (Janszky *et al.*, 2006).

By comparison, motor manifestations associated with T+ epilepsies consisted in more elementary motor signs, either tonic or versive. Thus, a statistically significant association with T+ epilepsies was found for ipsilateral tonic motor signs, without correlation to any of the T+ subgroups. Ipsilateral tonic motor signs have been reported during frontal lobe seizures (Janszky *et al.*, 2001), a finding which, although rare, is in accordance with the results of frontal lobe electrical stimulations (Lim *et al.*, 1994; Chauvel *et al.*, 1996). We therefore suggest that this sign, in the context of TL epilepsy, may point to the simultaneous involvement of temporal and extratemporal (possibly frontal) areas. In any case, it seems to have a better localizing significance than the classical dystonic posturing for distinguishing TL epilepsies from T+ epilepsies. This finding is consistent with the study of Bleasel *et al.* (1997) who failed to find a statistically significant difference for this sign between TL and extra-temporal seizures. Versive manifestations of the eyes and head, also, were more frequently associated to T+ epilepsies, which is in agreement with the extratemporal (either frontal or posterior) localizing significance of this sign (Salanova *et al.*, 1992; Williamson *et al.*, 1992; Manford, 1996; Bleasel *et al.*, 1997; Janzsky *et al.*, 2001). However, it has been observed also in seizures of TL origin (Wyllie *et al.*, 1996) and in this last case, our data suggest the need for caution before ascertaining that seizures arise from the TL only, especially when the movement is contralateral to the side of seizure onset, and also when it is associated with anxiety (see cluster 9, Table 3). This is in agreement with an ictal SPECT study of TL seizures showing that some ictal clinical symptoms, such as head version, are related to multiple hyperperfusion areas in the frontal, temporal and basal ganglia regions (Shin *et al.*, 2002).

Post-ictal signs

Post-ictal amnesia, although frequently found in both groups, was significantly associated with TL epilepsies,

a finding which might parallel to the preponderance of left-side seizures in the TL group. We cannot exclude, indeed, that the speech disturbances occurring at seizure onset and/or in the post-ictal phase can have made difficult the assessment of an eventual aura. However, there was no difference for post-ictal language deficits between TL and T+ groups, so that this hypothesis remains unlikely. Alternatively, the preponderance of post-ictal amnesia might be explained by a more frequent contralateral spread of the seizures in TL patients than in T+ patients, as suggested by some studies having showed that lack of aura experience strongly correlates with indicators of bitemporal dysfunction (Schulz *et al.*, 1995, 2001). In such a hypothesis, the fact that post-ictal amnesia might be especially relevant when associated with chewing automatisms (cluster 28, Table 3) could suggest that the amygdala, which seems to play a pivotal role in the occurrence of ictal chewing (Bancaud, 1997), might also play an important role for rapid bilateralization of TL discharges. However, the issue of contralateral seizure spread was not specifically addressed in the present study, and other explanations may exist, such as the role of the frontal EEG slowing observed during TL seizures (Blumenfeld *et al.*, 2004).

By opposition, post-ictal dysphoric changes were associated with T+ epilepsies, an interesting result which raises different—but unsolved—issues. First, this finding might be partly explained by the more frequent right lateralization of T+ epilepsies, which, however, remains matter of controversies (Kohler *et al.*, 1999; Quigg *et al.*, 2003; Helmstaedter *et al.*, 2004). Second, it might be related to a possible higher rate of interictal psychiatric symptoms in T+ patients. Kanner *et al.* (2004) found that the severity of interictal psychiatric and cognitive symptoms commonly worsened during the post-ictal period, and TL patients exhibiting such an evolution may be at higher risk of not being seizure free after TL surgery (Kanner, personal communication). We cannot confirm this interesting hypothesis as, in our patients, data about pre-operative psychiatric disturbances were not collected. Third, the post-ictal dysphoric changes could be equivalent to a 'Todd paralysis' engaging structures in the limbic system and prefrontal cortex, as proposed by Tombini *et al.* (2004). Even if we did not find any difference among the three subgroups of T+ patients, this issue remains of interest. Last but not least, our data might have some relevance in relation to a possible increased risk of post-operative psychiatric disorders in T+ patients in comparison to TL patients.

Scalp-EEG findings

In the present study, neither TL interictal spikes, nor TL ictal EEG onset, allowed us definitely to rule out the possibility of T+ epilepsy. This is in line with the study of Aghakani *et al.* (2004) who found that despite well-defined focal anterior and inferomesial temporal epileptic discharges, seizures may arise outside the TL. Conversely, T+ patients more frequently exhibited some interictal and ictal scalp-EEG patterns that might be helpful in deciding whether to perform invasive recordings or not. T+ patients more frequently showed precentral interictal abnormalities, topographically different from the fronto-temporal blunt sharp waves described in mesial-temporal lobe epilepsies (Wieser *et al.*, 2004). Despite their location, these abnormalities were not specific to one of the T+ subgroups. Additionally, T+ patients more frequently exhibited bilateral interictal abnormalities, which have been previously associated with a worse surgical outcome in TLE (Schulz *et al.*, 2000; Sylaja *et al.*, 2004). Also, the location of the first ictal EEG changes outside the borders of the temporal lobe was significantly associated with T+ epilepsies. These latter changes even allowed us to distinguish the three T+ subgroups, since frontal anterior, fronto-precentral and temporo-parietal ictal EEG onsets were more frequently and significantly associated with the TF subgroup, TS subgroup and TPO subgroup, respectively. These ictal findings are in line with previous reports which demonstrated that ictal onset located either posteriorly in the temporal lobe (Prasad *et al.*, 2003), or outside the temporal lobe, are predictive factors for failures of a temporal lobectomy (Barry *et al.*, 1992; Velasco *et al.*, 2000).

Conclusions

Our results, even if not conclusive, confirm that some ictal clinical signs, especially when found in specific clusters, as well as some interictal and ictal EEG abnormalities, can allow to suspect T+ epilepsy in the context of TL epilepsy, even in the case of hippocampal sclerosis. These findings may be useful for identifying, among patients suffering from 'atypical' TL epilepsy, those who should undergo invasive recordings before surgery. This might be significant for post-operative prognosis, providing that the whole epileptogenic area can be safely removed.

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