

Electro-clinical correlation between seizures induced by direct electrical cortical stimulation and spontaneous seizures: relevance to define the epileptogenic zone

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Electro-clinical correlation between seizures induced by direct electrical cortical stimulation and spontaneous seizures: relevance to define the epileptogenic zone

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DIPLÔME D'ÉTAT

TARDY Nastasia

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Monsieur de Professeur Philippe Kahane, Président du jury
Monsieur le Professeur Fabrice Bartolomei
Monsieur le Professeur Stéphan Chabardes
Monsieur le Professeur Olivier David
Monsieur le Professeur François Dubeau
Madame le Docteur Lorella Minotti, directrice de thèse

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Introduction

The primary aim of epilepsy surgery is to remove the epileptogenic zone (EZ), i.e. 'the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom' **(Rosenow and Lüders, 2001).** In this context, intracranial EEG (iEEG) can be performed when non-invasively obtained data remain insufficiently concordant, when they are discordant or inconclusive, or when they suggest an early involvement of highly eloquent areas **(Jayakar et al., 2016).** Such recordings aim not only at precisely identifying the cortical areas to be removed, but also at evaluating their functional integrity. This needs on the one hand the recording of spontaneous seizures, and on the other hand the use of cortical electrical stimulation (CES) to map eloquent cortical areas that will have to be spared during surgery.

Although the iEEG definition of the EZ mainly relies on the recording of spontaneous seizures (SS), some teams, mainly in France and Italy, routinely use CES during stereotactic iEEG (SEEG) recordings to aid in delineating the EZ, providing that the patient's typical electro-clinical pattern is produced (**Kahane et al., 2006**; **Trébuchon and Chauvel, 2016**). This approach, promoted by the Hospital Sainte Anne school **(Bancaud and Chauvel, 1986)**, is considered as a necessary complement of SS recording, particularly when spontaneous ictal discharges are widely extended from the onset, when they apparently arise independently from different brain structures, or when regions that are initially silent at seizure onset abruptly activate in the course of the ictal discharge. The clinical utility of CES-induced seizures (CESS), however, remains controversial and most of north-american centers using subdural electrodes do not rely on such information because they consider and CES-induced afterdischarges and seizures as a by-product of cortical mapping that can disrupt the procedure (**Bank et al., 2014**), may inaccurately localize cortical functions (**Blume et al., 2004**), and do not show consistent colocalization between the stimulation site

and the SS onset area (**Blume et al., 2004**). This controversy is partly linked to the great variability in the methodologies used across centers, to the lack of a consensual definition of CESS, and to the differences in the conceptual approach to epilepsy surgery.

Suprisingly and despite decades of intra- and extraoperative CES procedures in epilepsy surgery candidates, only a few studies have investigated the relevance of CESS in clinical practice. In a recent review, 14 studies were identified during a 30 years period (1974-2004), of which 9 used SEEG electrodes, 3 intraoperative CES, and 2 subdural electrodes (**Kovac et al., 2016**). Overall, the percentage of patients in whom seizures could be elicited varied from 37 to 100%, with a large predominance of CES-elicited auras. The concordance rate between the electrodes exhibiting CESS and those overlying the site(s) of SS onset, evaluated in only 6 of these 14 studies, varied from 26% to 100%, with the best results obtained in patients with focal cortical dysplasia or suffering from temporal lobe epilepsy (**Bernier et al., 1990**; **Chassoux et al., 2000**; **Chauvel et al., 1993**; **Landré et al., 2004**; **Schulz et al., 1997**; **Wieser et al., 1979**). How the information obtained from CESS might influence seizure outcome was assessed in only one study, that did not show any differences according to whether CESS site(s) were included in the resection or not (**Schulz et al. 1997**). Based on these existing data, it thus appear that further studies are needed to better evaluate the clinical and iEEG overlap beween SS and CESS, and to determine what is the precise added contribution of CESS over SS in terms of seizure outcome. The present retrospective study aimed at answering these issues in a series of 30 consecutive patients who underwent SEEG recordings at our institution. Whether general features might influence the information provided par CESS was also evaluated.

Patients and methods

Patients selection

Between October 2013 and November 2015, 32 patients suffering from drug-resistant focal seizures underwent a SEEG study at Grenoble-Alpes University Hospital as part of their presurgical evaluation. For the purpose of the study were selected the 30 patients in whom at least one complete spontaneous electro-clinical seizure was recorded during SEEG investigation.

Patients's characteristics

The 30 patients were all suffering from drug-resistant focal epilepsy, the operability of which could not be decided on the basis of non-invasive procedures only. These latter included in all cases high-resolution MRI, scalp-video-EEG monitoring, and neuropsychological tests. Some patients underwent also functional neuroimaging.

A summary of the patients' characteristics is given in Table 1. Briefly, there were 15 males and 15 females, whose mean age at SEEG investigation was 28 years (range 9-59 years). Mean age at seizure onset was 15 years (range 0.5-38 years), and mean duration of epilepsy was 14 years (range 3-40 years). MRI demonstrated different kind of lesions in 21 patients, of whom 6 had previously undergone unsuccessful resective surgery before SEEG procedure. MRI was negative in 9 cases.

Pt	Sex	Age at SEEG (years)	Epilepsy onset/duration (years)	MRI findings	Surgery	Number of SEEG electrodes	Histology	Outcome (Engel's class)	Follow-up (months)
1	M	41	4 / 37	R F FCD	R F (mesial)	13 L	FCD IIb	IA	16
2	F	11	8 / 3	N	R T (antero-mesial)	13 R / 5 L	Heterotopic neurons	IB	15
3	M	48	38 / 10	R HS	No (bi-T)	9 R / 7 L	NA	NA	NA
4	M	34	24 / 10	Bilateral PVNH	L T (antero-mesial)	4 R / 10 L	Heterotopia	IA	3
5	M	28	25 / 3	R F tumor residue *	R F (mesial)	12 R	Oligodendroglioma	IA	3
6	M	28	12 / 16	L posterior PVNH	L T-P RFTC	13 L	NA	IVB	3
7	M	29	25 / 4	R F tumor residue *	R F (basal)	15 R	DNET	IA	9
8	M	12	6 / 6	L FCD	L F (mesial)	15 L	FCD IIb	IA	14
9	M	59	37 / 22	L F scar *	L F (basal)	12 L	Gliosis	IA	3
10	M	14	1 / 13	L F scar *	L T-Ins	14 L	MMCDOH	IVB	8
11	F	31	28 / 4	N	R F (basal)	15 R	FCD IIb	IA	3
12	F	47	7 / 40	N	No (bi-multifocal)	10 R / 6 L	NA	NA	NA
13	F	23	4 / 19	L P atrophy	L F-P (mesial)	15 L	FCD Ia	IVB	2
14	F	15	12 / 3	L T polar blurring	L T (basal)	15 L	Gliosis	IIIA	12
15	F	31	24 / 7	N	L T (antero-mesial)	11 L	Heterotopia	IA	4
16	M	16	7 / 9	N	L Ins RFTC	7 L	NA	IID	28
17	F	15	7 / 8	R T polar blurring	R T-Ins-opercular	16 R	FCD IIIa	IVB	19
18	M	32	21 / 11	N	No (bi-T)	12 R / 4 L	NA	NA	NA
19	F	33	14 / 19	L Ins-opercular scar	L Ins RFTC	17 L	NA	IIIA	29
20	F	13	10 / 3	R F FCD	R F (lateral)	16 R	FCD Ia	IA	19
21	M	26	10 / 16	L F scar *	L F (mesial)	4 R / 12 L	Gliosis	IID	5
22	M	37	4 / 33	L T Scar *	L F (basal)	2 R / 11 L	FCD Ia	IB	14
23	M	48	12 / 36	N	R T (antero-mesial)	15 R	FCD IIb	IA	24
24	F	20	12 / 8	HS	L T (antero-mesial)	5 R / 10 L	FCD IIIa	IA	28
25	F	42	13 / 29	N	L T (antero-mesial)	3 R / 10 L	HS	IA	19
26	F	24	10 / 14	Polymicrogyria	R T-C	14 R	FCD Ia	IVA	31
27	M	14	0.5 / 14	R-T-P cortical thickness	R-T-P (lateral)	15 R	FCD Ia	IV B	18
28	F	26	20 / 6	N	L F (mesial)	14 L	Gliosis	IA	28
29	F	45	42 / 3	N	L T (antero-mesial)	11 L	FCD IIIa	IA	38
30	F	9	7 / 2	N	L F (mesial)	16 L	FCD Ia	IA	3.2

Table 1: Patient's characteristics. Patients who experienced at least one CES-elicited electro-clinical seizure are highlighted in grey (n=24). Pt: patient number; M: male; F:female; N: normal; R: right; L: left; F: frontal; T: temporal; P: parietal; C:central; Ins: insular; O: occipital ; DNET: dysembryoplasic neuroepithelial tumor; FCD: focal cortical dysplasia; HS: hippocampal sclerosis; MMCDOH: mild malformation of cortical developement with oligodendroglial cells; PVNH: pervicentricular nodular heterotopia; RFTC: radiofrequency thermocoagulation; NA: not applicable; [1] previously operated (#5: R F oligodendroglioma; #7: R F DNET; #8: L F cavernoma; #10: L F resection/disconnection (negative histology); #21: L F resection with negative MRI; #22: L T disconnection with negative MRI).

SEEG investigation

Twelve to 18 (mean: 14.3) multicontact semirigid intracerebral electrodes were implanted in each patient in stereotaxic conditions, according to the SEEG methodology developed in our group **(Kahane et al., 2004)**. Electrodes placement and number was tailored in each individual depending on the suspected origin of seizures. Preoperative targeting was performed using 3-D T1 brain MRI computed with a stereotactic software (ROSA stereotactic assistance®), and using a stereotaxic and stereoscopic digitalized arteriography to determine avascular trajectories of the electrodes. Insertion of the electrodes (DIXI Medical, Besançon, France; diameter of 0,8 mm; 10 to 18 contacts, 2 mm length, 1.5 mm apart) was guided by a robotic arm (Medtronic O-Arm®) that was connected to the stereotactic frame and driven by the stereotactic software. Electrodes contacts were visualized directly on post-implantation MRI, and/or after a computer-assisted matching of post-implantation CT-scan with a pre-implantation 3D MRI.

SEEG recordings were conducted extra-operatively for about 2 weeks with reduced medication in 23 of the 30 patients, using an audio-video-EEG monitoring system (MicromedTreviso, Italy) that allowed to record simultaneously up to 128 contacts, with a sampling rate of 512 Hz and an acquisition band-pass filter between 0.1 and 200 Hz. Data were acquired using a referential montage, with a reference electrode chosen in the white matter. SEEG activity was displayed between contiguous contacts at different levels along the axis of each electrode, and interictal and ictal analysis of SEEG traces was done visually.

CES were performed for a few days during one to three hour sessions, according to our routine procedure (**Kahane et al., 1993**). The aim was to reproduce part or the totality of the ictal clinical symptomatology, and to localize functionally eloquent areas that had to be spared during surgery. Bipolar stimuli were delivered using a constant current rectangular pulse generator designed for a safe diagnostic stimulation of the human brain (Micromed, Teviso, Italy). Bipolar CES were performed at 1 Hz (pulse width: 1msec; ES duration: 40 sec)

and 50 Hz (pulse width: 0.5-1ms; ES duration: 5 sec), and applied between all contiguous contacts located in the cortex, with stepwise increasing intensities up to 5 mA and until clinical responses, after-discharges or seizures were obtained.

Following SEEG results, 17 patients had a left-sided, 10 a right-sided, and 3 a bilateral focal epilepsy (Table 1). The epilepsy was unilobar in 21 cases (frontal: 11, temporal: 8, insular: 2), multilobar in 6 (temporo-parietal: 2, temporo-central: 1, temporo-insular: 1, temporo-insulo-opercular: 1, fronto-parietal: 1), bitemporal in 2, and bilateral multifocal in 1.

Surgery

Surgery, including radiofrequency thermocoagulation (RFTC), was performed in all but 3 cases, according to SEEG results (Table 1). The extent of the resection/RFTC was assessed on a 3-D T1 post-operative MRI usually performed 3 months after surgery. After a mean post-operative follow-up of 15 months (range: 2-38 months), 17 patients (63%) were in class I according to Engel's classification, 2 in class II (7.4%), 2 in class III (7.4%), and 6 in class IV (22.2%). Pathological examination, available in all the 24 resective cases, found different kind of lesions in 13 of the 16 patients whose MRI proved positive, and in 7 of the 8 patients without any abnormality on MRI.

Data analysis

Spontaneous seizures

All SEEG-recorded SS were reviewed, but neither subclinical seizures, nor seizures in which auras occurred without any SEEG modification were kept for analysis.

The EZ was defined according to its electrophysiological definition, i.e. the ‘‘site of the beginning and of the primary organization of the epileptic seizures’’ **(Munari and Bancaud, 1987).** The EZ therefore included the seizure onset zone (the region exhibiting the first SEEG change that occurred prior to, or concomitant with, the clinical onset of the seizure) as well as

the region of early seizure spread (that was arbitrarily defined as the region involved by the SEEG discharge within the first 20 seconds following the ictal onset). SEEG changes at seizure onset were classified, whatever possible, according to the seizure-onset patterns proposed by **Perucca et al. (2014)**.

The anatomical extent of the EZ was evaluated in each patient by the number of electrode contacts involved during the first 20 seconds of the SS. If different seizure patterns were recorded, all the contacts involved within the first 20 seconds, whatever the seizures, were included in the EZ.

Seizure semiology was analyzed according to a working definition of clinical phenomena derived from the classification of **Lüders et al.** (**1998**). Briefly, a total number of 6 core clinical signs were systematically evaluated, including aura, autonomic signs, loss of contact, simple motor signs, complex motor signs and negative phenomena. They were quoted as present or absent in each SS, and they were then compiled in a single list for all SS.

CES-elicited seizures

Only CES-induced electro-clinical seizures were analysed, and neither elicited isolated aura (without SEEG discharge), nor isolated after-discharges (without clinical accompaniment), were considered in the present work.

CESS thus referred to electro-clinical events that occurred as an immediate result of CES, and in which both clinical signs and SEEG discharge outlasted the electrical stimulus. They were considered as habitual (non habitual) when elicited clinical manifestations were (were not) recognized by the patient and/or his/her relatives.

The parameters used to elicit CESS were first evaluated. Then, the CESS onset patterns, anatomical extent of the elicited discharges, and CESS semiology were assessed using the same criteria than those used for SS analysis. Whether the CES location within or outside the EZ might influence the rate of CESS was also evaluated.

Comparison between SS and CESS

A rate of electrical concordance was calculated for each patient by comparing the extent of the EZ with the mean extent of all elicited discharges. Similarly, a rate of clinical concordance was evaluated in each patient by comparing the mean number of clinical signs observed during CESS with the list of SS clinical signs.

Still, whether other factors might influence the rate of electrical and/or clinical concordance was assessed. These factors included the age at seizure onset, epilepsy duration, MRI findings (negative versus positive), and epilepsy type (temporal versus extra-temporal).

CESS and outcome

All the post-operative MRI were reviewed to evaluate, for each patient, the percentage of CESS contacts that were located in the resective (or thermo-coagulated) area. This percentage was then compared with post-operative seizure outcome.

Other potential prognosis factors were also evaluated, including the number of CESS, the percentage of contacts that elicited CESS within the EZ, the SEEG LVFA pattern at CESS onset, and the rates of electrical/clinical concordance.

Statistics

We used Fisher's exact test for categorical data, and Mann-Whitney's U test or Spearman's correlation for continuous data. Significance was set at $p \leq 0.05$.

Results

Twenty four of the 30 patients (80%) exhibited at least one CESS. Their general characteristics did not seem to differ from the ones of the 6 patients who did not present any CESS (Table 1). None of these later, however, were suffering from temporal lobe epilepsy (TLE), as compared with 10 of the 24 patients with CESS.

The following sections will refer only to these 24 patients, who exhibited both SS and CESS.

Pt	N° of SS	N° of contacts involved in the EZ	N° of CESS (CS)	N° of CESS elicited by CES of the EZ (CS)	Mean N° of contacts involved during CESS (CS)	Mean N° of CESS contacts located in the EZ (CS)	Percentage of electrical correlation between SS and CESS (CS)	Percentage of clinical correlation between SS and CESS (CS)	N° of contacts eliciting CESS		Engel's class
									All	Resected	
1	2	17	2 (1)	2 (1)	8 (7)	8 (7)	100 (100)	75 (75)	2	1 (50%)	IA
2	3	8	7 (1)	3 (0)	6 (8)	3.6 (7)	59.5 (70)	88.9 (60)	7	3 (43%)	IB
3	3	25	2 (2)	2 (2)	15 (15)	10 (10)	66.7 (66.7)	100 (100)	2	no surgery	na
4	5	30	8 (0)	7 (-)	11 (-)	7.4 (-)	67 (-)	100 (-)	8	8 (100%)	IA
5	3	6	2 (1)	1 (0)	4 (5)	3.5 (4)	87.5 (80)	100 (100)	2	1 (50%)	IA
6	3	34	1 (1)	0 (0)	13 (13)	11 (11)	84.6 (84.6)	100 (100)	1	1 (100%)	IVB
7	2	6	1 (1)	0 (0)	10 (10)	3 (3)	30 (30)	100 (100)	2	0 (0%)	IA
8	12	27	13 (2)	11 (1)	10.8 (26.5)	10.6 (26.5)	98.6 (100)	25 (25)	10	4 (40%)	IA
11	18	47	1 (1)	1 (1)	21 (21)	21 (21)	100 (100)	100 (100)	1	1 (100%)	IA
12	4	37	1 (0)	0 (-)	12 (-)	7 (-)	58.3 (-)	33 (-)	1	no surgery	na
13	193	34	2 (2)	0 (0)	12 (12)	11 (11)	91.7 (91.7)	100 (100)	2	0 (0%)	IVB
14	70	19	12 (0)	9 (-)	6.2 (-)	3.4 (-)	55.4 (-)	92.3 (-)	10	2 (20%)	IIIA
15	14	18	5 (2)	4 (2)	9 (9)	4.6 (6)	51.1 (66.7)	100 (100)	4	2 (50%)	IA
16	1	18	7 (0)	7 (-)	12.6 (-)	10 (-)	79.5 (-)	100 (-)	7	3 (43%)	IID
18	17	46	4 (1)	3 (0)	18.2 (48)	13 (34)	71.2 (70.8)	85.7 (100)	3	no surgery	na
19	2	15	3 (2)	0 (0)	16.3 (17.5)	6.3 (6.5)	38.8 (37.1)	- *	4	2 (50%)	IIIA
20	9	47	1 (0)	1 (-)	4 (-)	4 (-)	100 (-)	100 (-)	1	0 (0%)	IA
23	12	14	4 (1)	3 (1)	14.5 (10)	10 (10)	67.7 (100)	100 (100)	4	2 (50%)	IA
24	13	15	6 (0)	4 (-)	13.8 (-)	8.8 (-)	63.8 (-)	100 (-)	6	3 (50%)	IA
25	20	74	1 (1)	1 (1)	48 (48)	48 (48)	100 (100)	66.7 (66.7)	1	1 (100%)	IA
26	2	12	1 (0)	0 (-)	11 (-)	0 (-)	0 (-)	0 (-)	10	2 (20%)	IVA
27	13	54	1 (0)	1 (-)	2 (-)	2 (-)	100 (-)	100 (-)	7	1 (14%)	IVB
28	11	72	4 (1)	4 (1)	15.7 (20)	15.7 (20)	100 (100)	83.3 (100)	4	2 (50%)	IA
29	1	23	10 (3)	5 (3)	3.2 (62.3)	1.2 (20)	37.3 (32.1)	100 (100)	10	6 (60%)	IA

Table 2: Comparison between stimulation-induced and spontaneous electro-clinical seizures. Patients who experienced at least one complete CES-elicited electro-clinical seizure are highlighted in grey (n=16). Pt: patient; SS: spontaneous seizures; EZ: epileptogenic zone; CESS: electro-clinical seizures elicited by CES (cortical electrical stimulation); CS: complete electro-clinical seizures elicited by CES; * no video material available; na: not applicable.

Spontaneous seizures (SS) *(Tables 1 and 2)*

A total number of 402 SS (mean: 16.7/patient; range: 1-193) was recorded in the 24 patients. Six to 74 contacts per patient were part of the EZ (mean: 29), which was temporal in 10 patients (mesial: 7, temporo-basal: 1, bitemporal: 2), frontal in 7 patients (mesial: 4, fronto-basal: 2, lateral: 1), insular in 2 patients, and multilobar or multifocal in 5 patients.

Most SS started with a low-voltage fast activity (LVFA, n=270, 67%) (Figure 1a). The other seizure onset patterns included a fast discharge or spikes or polyspikes (FDS, n=68, 17%), a mixture of LVFA and FDS, (n=50, 12%), a rythmic spikes or spike-and-waves discharge (RSD, n=13, 3%)**,** and a rythmic alpha-theta sharp activity (RSA, n=1, <1%)**.**

CES-elicited electro-clinical seizures (CESS) *(Tables 1, 2 and 3)*

A total number of 99 electro-clinical seizures (mean: 4.1/patient; range: 1-14) were elicited by CES in the 24 patients, of which 76 (in 22 patients, mean: 3.4/patient) were clinically characterized by auras (77%), and 23 (in 16 patients, mean: 1.4/patient) by complete seizures (CS, 23%). CES-elicited aura was the main seizure type in TLE (48/59), insular epilepsy (ILE, 8/10), and frontal epilepsy (FLE, 17/24), but not multilobar/multifocal epilepsy (MLE, 3/6) epilepsy.

Five of the 76 auras (in 5 patients) and 4 of the 23 CS (in 4 patients) were reported by the patients as non habitual seizures (NHS). (Figure 2b) All but one were observed in TLE cases, while the remaining one occurred in an ILE case. Six of the 9 NHS, however, were considered by the observers as quite similar to the SS recorded during the video-(S)EEG monitoring. Thus, only 3 of 99 CESS (3%) raised the issue of 'false positive' electro-clinical events; they were elicited in 2 patients with TLE (#24, #25) and in one patient with ILE (#19).

CESS were more frequently induced using 50Hz CES (n=77, 77.8%) than using 1Hz CES (n=22, 22.2%), but the difference did not reach statistical significance (p=0.27, Fisher's exact test). Also, the intensity used to elicit CESS was lower with 50Hz than with 1Hz stimulation, without any significant association (p=1, Fisher's exact test). 50Hz CES induced more

commonly CS (20/77, 26%) than 1Hz CES did (3/22, 13.6%), but they were also more prone to elicit NHS (8/9 NHS after 50 Hz CES versus 1/9 after 1 Hz CES, p=0.68, Fisher's exact test).

In comparison with SS, the elicited discharges started more frequently with a FDS (n=78, 65%) than with a LVFA (n=13, 16%) (Figure 1bc). The other ictal patterns included LVFA+FDS (n=5, 14%), and RSA (1, 1%). Elicited RSD was never observed.

Sixty nine of the 99 CESS (70%), and 13 of the 23 CS (13/23, 56.5%), were elicited by a contact located within the EZ.

	Pts	CESS	Epilepsy type				1Hz CES		50Hz CES	
	n°	n°	TLE (Pts)	FLE (Pts)	ILE (Pts)	MLE (Pts)	n°	intensity (mA)	n°	intensity (mA)
All	24	99	59 (10)	24 (7)	10 (2)	6 (5)	22	2.9 (1-5)	77	2.2 (0.4-5)
Aura	22	76	48 (10)	17 (7)	8 (2)	3 (3)	19	2.9 (1-5)	57	2.2 (0.4-5)
CS	16	23	11 (8)	7 (5)	2 (1)	3 (2)	3	3.0 (3-3)	20	2.3 (1-5)
NHS *	8	9	8 (7) **	0	1 (1) ***	0	1	3	8	2.4 (2-3)

Table 3: General characteristics of stimulation-induced electro-clinical seizures. Pts: patients; n°: number; CES: cortical electrical stimulation; CESS: electro-clinical seizure elicited by CES; : aura: electro-clinical aura elicited by CES; CS: complete electro-clinical seizure elicited by CES; NHS: non habitual electro-clinical seizure elicited by CES; * 5 (in 5 pts) were part of auras, and 4 (in 4 pts) were part of CS; ** 5 (in 5 pts) were part of auras, and 3 (in 3 pts) were part of CS; *** this event was part of CS; TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; ILE: insular lobe epilepsy; MLE: multilobar/multifocal epilepsy.

Electro-clinical comparison between SS and CESS *(Tables 2 and 3)*

SEEG findings were available in all the 24 patients. Overall, 1312 contacts were involved within the first 20 seconds of all the CESS (mean number/patient: 3.2-48), of which 854 (70.4%) (mean number/patient: 0-48) overlapped with the EZ. The rate of electrical concordance varied from 0 to 100% per patient, with an average of 77.4%. This concordance

rate was even better when considering only the CS, with a mean of 86.7% per patient (30-100%) (Figure 1abc).

Seizure semiology was available in all but one patients, in whom the video material of the unique seizure recorded could not be visualized (#19). For the remaining 23 patients, 126 (85.1%) of the 148 clinical signs identified during CESS (1-21/patient) were concordant with those identified during SS. As for electrical findings, the rate of clinical concordance was higher for CS (n=15 patients, mean: 95.3%, range: 25-100%) than for the whole group of CESS (mean: 85.1%, range: 0-100%).

No statistically significant association was found between the rates of electrical/clinical concordance and (i) the age at seizure onset (p=0.14/0.09, Spearman's correlation), (ii) epilepsy duration (p=0.44/0.33, Spearman's correlation), (iii) MRI findings (p=0.67/0.33, Mann-Whitney's U test), and (iv) epilepsy type (p=0.15/0.67, Mann-Whitney's U test).

CESS and seizure outcome

Overall, the percentage of contacts that elicited seizures and which were located in the resective (or thermo-coagulated) area varied from 0% to 100% per patient (mean: 43.7%) for all CESS, and from 0% to 100% (mean: 48%) for CS only. These percentages did not significantly correlated with the post-operative seizure outcome (respectively p=0.24 and p=0.74, Mann-Whitney's U test).

Otherwise, no statistically significant association was found between seizure outcome and (i) the number of CESS (p=0.26, Mann-Whitney's U test, (ii) the percentage of contacts that elicited CESS within the EZ (p=0.24, Mann-Whitney's U test), (iii) the SEEG pattern of LVFA at CESS onset (p=1, Fisher's exact test), and (iv) the rates of electrical/clinical concordance (p=0.96/0.45, Mann-Whitney's U test).

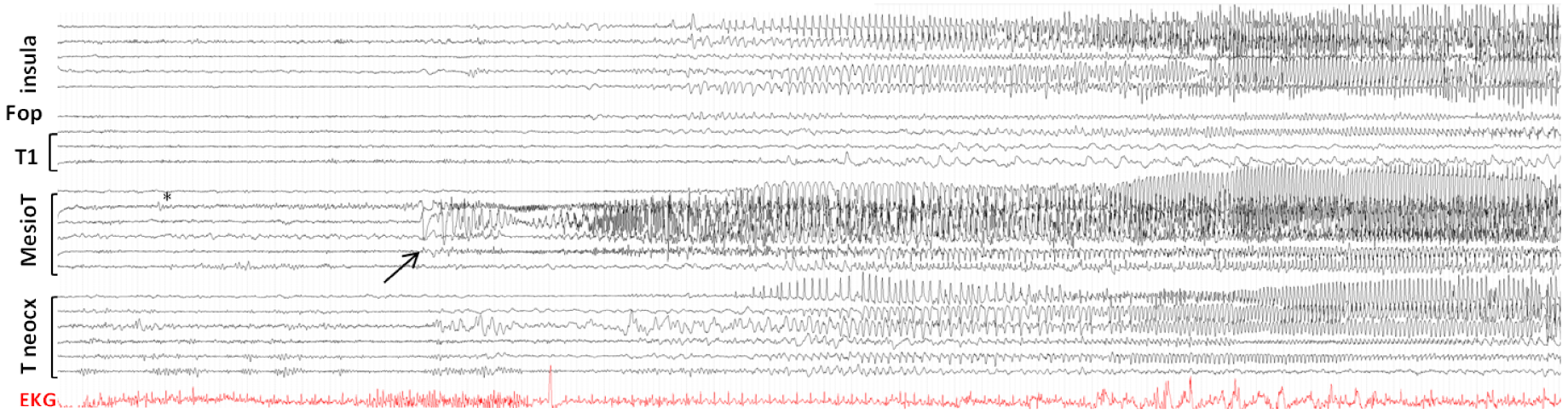


Figure 1a. Spontaneous seizure (patient 29). Low voltage fast activity (LVFA) involving first the amygdala (*), followed by a mixture of LVFA with a fast discharge of spikes within mesial temporal structures 12 seconds later (arrow). The discharge then propagate to the insula and temporal neocortex. Fop: frontal operculum; STG: superior temporal gyrus; MesioT: mesio-temporal structures; T neocortex: temporal neocortex. EKG: electrocardiogram.



Figure 1b. 1Hz-stimulated seizure, anterior hippocampus, 3mA (same patient as in Figure 1a). The spatial distribution and shape of the elicited discharge is similar to the spontaneous one. Clinical semiology is the same. Fop: frontal operculum; STG: superior temporal gyrus; MesioT: mesio-temporal structures; T neocortex: temporal neocortex. EKG: electrocardiogram.

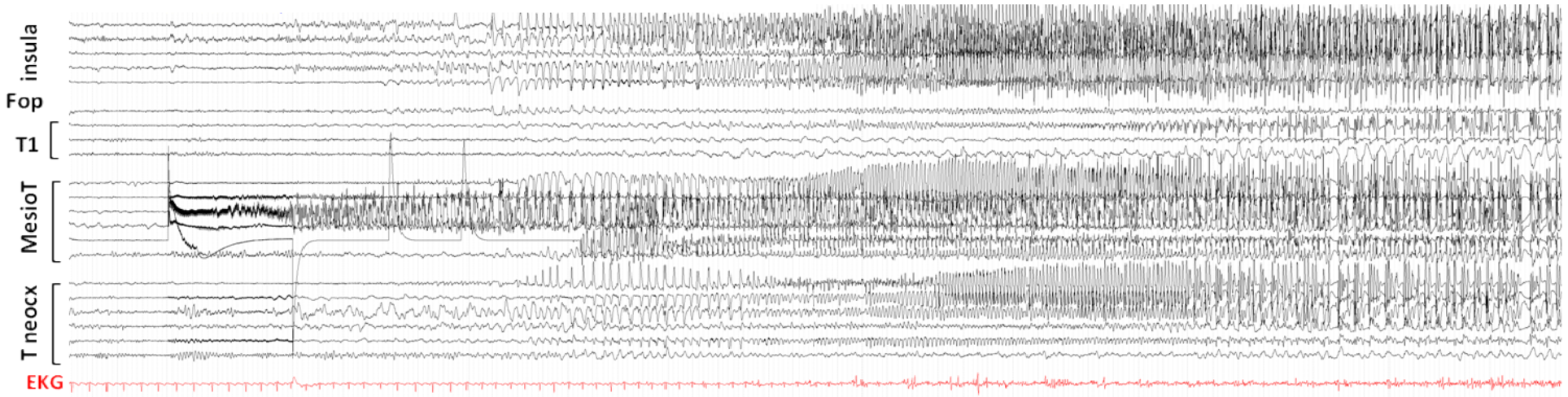


Figure 1c. 50Hz-stimulated seizure, entorhinal cortex, 2mA (same patient as in Figure 1ab). As compared with the spontaneous seizure (Fig.1a), the initial part of the elicited seizure is obscured by artefacts, the SEEG pattern consists from the onset in a fast discharge of spikes, and seizure spread faster, therefore explaining some clinical discrepencies (loss of contact from the onset and amnesia of the episode).



Figure 1d: **50Hz-stimulated seizure, temporal pole, 2mA:** the patient referred a chest warmth recognized as a part of her habitual seizure. The afterdischarge involves the mesial temporal structures, the anterior insula and the temporal neocortex with different electrical patterns than the spontaneous one, more tonic on the temporal pole (arrow).

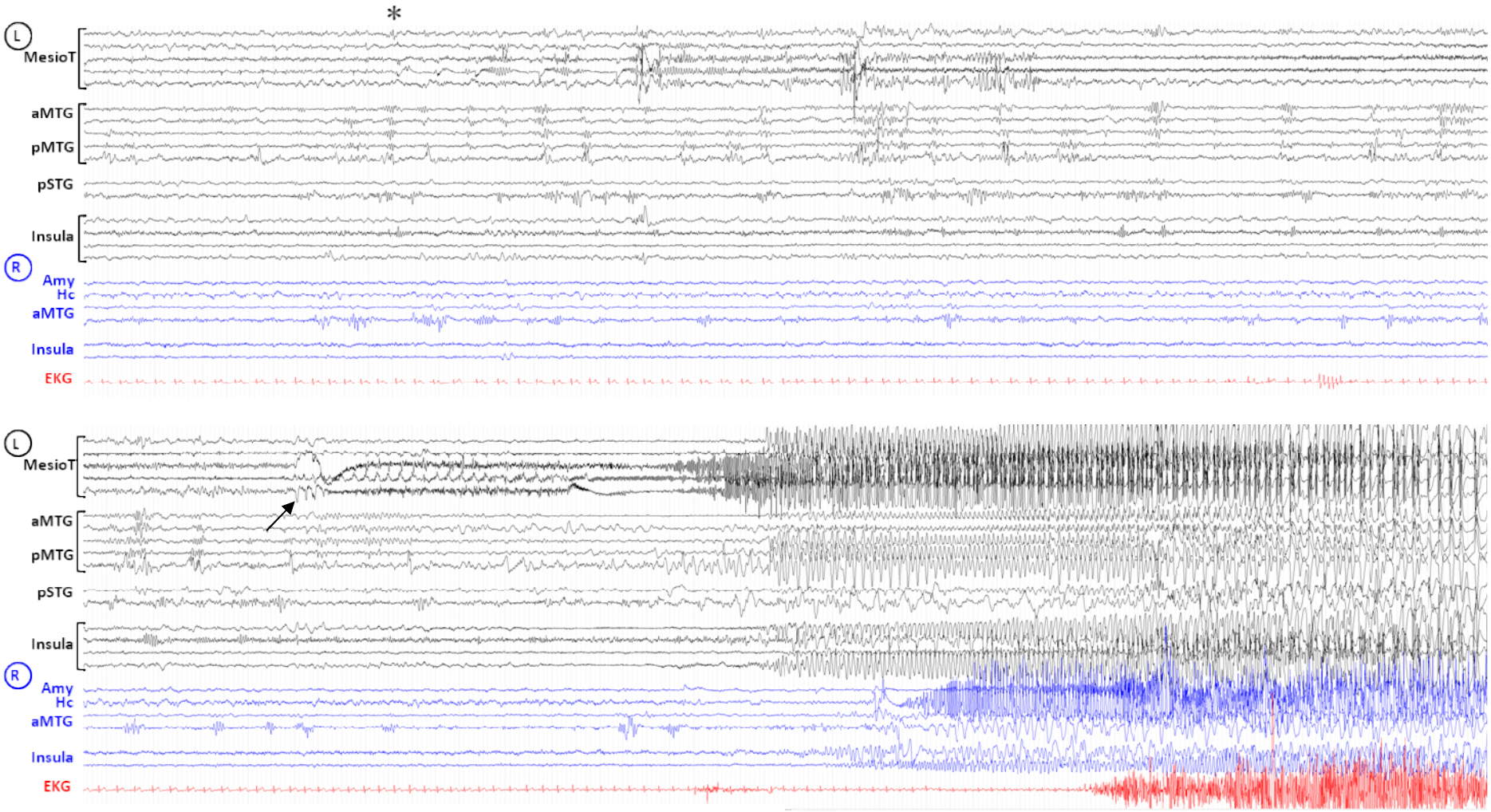


Figure 2a: spontaneous seizure: the discharge involves first (*) the left mesial temporal structures (mesioT), becoming more tonic and spreading (arrow) 54 seconds after the onset, to the left insular cortex, the left temporal neocortex (aMTG, pMTG, PSTG) and to the right mesial temporal structures (amygdala and hippocampus) and the right insula. L: left. R/right. MesioT: mesial temporal structures. aMTG: anterior middle temporal gyrus. pMTG: posterior middle temporal gyrus. pSTG : posterior first temporal gyrus. Amy: amygdala. Hc: hippocampus. EKG: electrocardiogram.

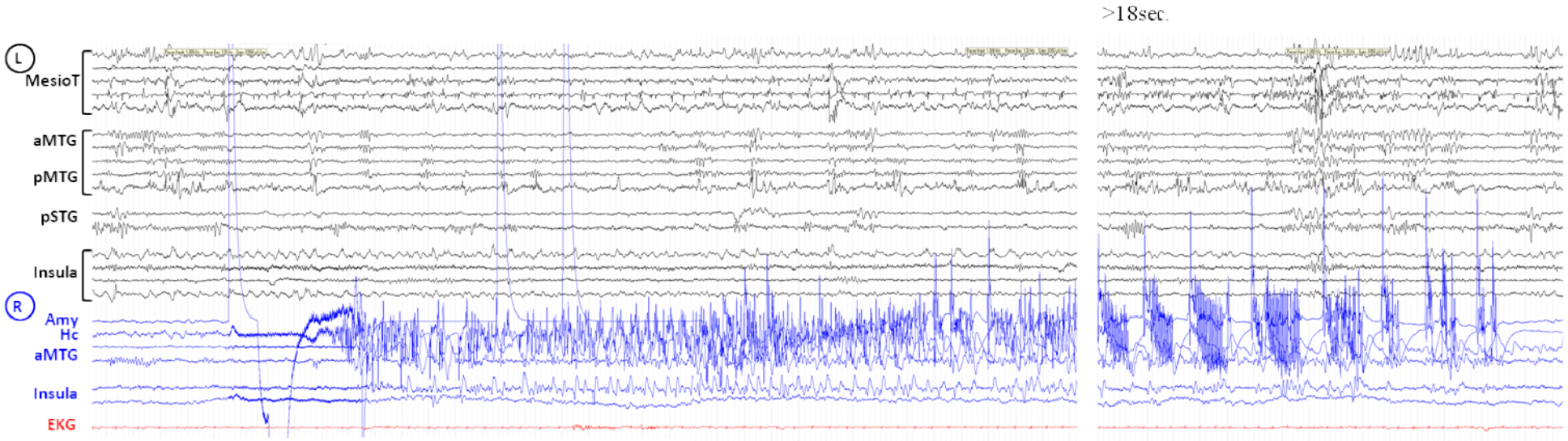


Figure 2b: **right amygdala 50Hz stimulation** : the afterdischarge involves the right amygdala and the right hippocampus and in a lesser extent the right insula, as in the second part of the spontaneous seizure.

Discussion

Since the pioneering works of Penfield and Jasper (**Penfield and Jasper, 1954**), CES has appeared as a powerful technique to study network mechanisms in epilepsy, including functional mapping of brain functions, estimation of functional connectivity, assessment of cortical excitability, and elicitation of seizures (**David et al., 2010**). This later aspect, however, has been poorly investigated (**Kovac et al., 2016**) and the main purposes of the present work were to evaluate how CESS and SS overlapped, both electrically and clinically, and whether the information obtained from CESS might help for the surgical decision. To this aim, attention was focused on electro-clinical events in order to rule out all the ambiguities raised by the elicitation of isolated auras (i.e., auras that are generated during the stimulation without concomitant nor further iEEG change), or by the induction of isolated afterdischarges (i.e., asymptomatic discharges of spikes, polyspikes or sharp waves that are directly related to and outlast CES, without evolving in frequency and spatial location).

CESS is not a rare phenomenon

In a recent review, the rate of CESS was shown to vary from 37 to 100%, depending on the type of CES procedure, on the criteria used to define CESS, and on the studied population (**Kovac et al., 2016**). Our study, conducted in an heterogenous population of consecutive patients, confirms that CESS ressembling to SS (i.e., electro-clinical CESS) can be found in a vast majority of patients submitted to SEEG recordings (24/30 patients, 80%), a rate which is close to the overall rate of CESS (343/449 patients, 76%) found in other studies conducted by means of intracerebral electrodes (**Bernier et al., 1990**; **Chassoux et al., 2000**; **Chauvel et al., 1993**; **Halgren et al. 1978**; **Kahane et al., 1993**; **Landré et al., 2004**; **Munari et al., 1993**; **Wieser et al., 1979**). By comparison, the overall rate of CESS observed intraoperatively (**Salanova et al., 1992**; **Salanova et al., 1995a,b**) or using subdural electrodes (**De Salles et al., 1994**; **Schulz et al., 1997**) has been shown to be much lower

(65/173, 38%), a finding that might be related to the use of electrodes that penetrate the cortex rather overlay it, as well as to the use of bipolar CES which delivers more localized current flows than unipolar CES does (**Nathan et al., 1993**).

As showed by others (**Landré et al., 2004**), our study also found that the temporal lobe was more sensitive than the frontal lobe for eliciting CESS, since all of the 10 stimulated TLE patients (of whom 8 were suffering from mesio-TLE) exhibited CESS, as compared with 7 of the 10 patients with FLE (see Table 1). Additionnally, CES of the insular lobe resulted in CESS in the 2 patients stimulated so far. Limbic structures therefore appear as particularly responsive to CES, which may in turn lead more frequently to NHS, as suggested by our results (all the NHS were elicited either in TLE or ILE patients).

Previous studies have showed that a large percentage of CESS clinically resulted in auras, that could be associated or not with iEEG changes (**Halgren et al., 1978**; **Kahane et al., 1993**; **Salanova et al., 1992**; **Salanova et al., 1995a,b**; **Schulz et al., 1997**). Most were elicited from the temporal lobe (**Halgren et al., 1978**; **Kahane et al., 1993**) or from the posterior cortex (**Salanova et al., 1992**; **Salanova et al., 1995a,b**). CS were less frequent and were observed in any locations, in particular when stimulating the frontal lobe (**Bancaud et al., 1974**). Using more strict criteria for defining CESS, we also found a large predominance of auras (77%) as compared with CS (23%). This over-representation of auras were found in all forms of epilepsies, except in MLE.

Whereas literature has showed that most CESS were elicited using high frequency (50-60Hz) CES, a few studies have reported the interest to use low frequency (1Hz) stimulation to elicit seizures (**Chassoux et al., 2000**; **Chauvel et al., 1993**; **Kahane et al., 1993**; **Landré et al., 2004**; **Munari et al., 1993**). 1Hz CES, indeed, allows a better visualization of the SEEG recording at the onset of the induced discharge and during the stimulation itself (see Figure 1b), though with a more uncertain effectiveness (**Kahane et al., 1993**; **Munari et al., 1993**). Our results confirms that 50Hz CES was more prone than 1Hz CES to elicit CESS (78%

versus 22%), especially for CS. However, 50Hz CES also accounted of most NHS (89%), which could thus limit its utility.

Are CES-induced seizures similar to the spontaneous ones?

A few studies have tried to evaluate the electrical and/or clinical similarities between CESS and SS, with an estimation of the concordance rate that varied between 26% and 100% (**Bernier et al. 1990**, **Chassoux et al., 2000**; **Chauvel et al., 1993**; **Landré et al., 2004**; **Schultz et al., 1997**; **Wieser et al., 1979**). Data analysis, however, face with many difficulties such as the lack of information on the number of stimulated electrodes (**Bernier et al., 1990**; **Chassoux et al., 2000**; **Chauvel et al., 1993**; **Landré et al., 2004**; **Wieser et al., 1979**), CES parameters (**Wieser et al., 1979**), type of epilepsy (**Bernier et al., 1990**), iEEG changes (**Schulz et al., 1997**), and type (auras versus complete seizures) of CESS (**Bernier et al., 1990**; **Chassoux et al., 2000**; **Chauvel et al., 1993**; **Landré et al., 2004**; **Wieser et al., 1979**). Still, some studies evaluated the concordance rate only in terms of seizure laterality (**Wieser et al., 1979**), or in specific situations such as focal cortical dysplasias (**Chassoux et al., 2000**).

Our study, despite some limitations, compared carefully both electrical and clinical correlates of SS and CESS. It showed that a strong electrical (77.4%) and clinical (85.1%) concordance with SS did exist for the whole group of CESS, that was even better (86.7% and 95.3%, respectively) after having excluded the elicited auras which were likely to activate only part of the EZ. This high rate of electro-clinical concordance, which was neither influenced by the age at seizure onset, duration of epilepsy, MRI data, and epilepsy type, therefore suggests that CES can reactivate accurately the cortical areas involved in spontaneous ictogenesis, and thus could be reliable enough to define the EZ. This assumption, however, must be softened based on the following elements: i) we chose arbitrarily the first 20 seconds of SEEG discharges to account for the extent of the EZ, which prevented us to analyse the whole seizures evolution;

we thus have possibly missed some late discordances between SS and CESS, or late activations of initially silent areas that were more relevant than those occurring as the immediate result of CES (Figure 2a,b) ii) As compared with SS, which started more frequently with a LVFA (i.e., the most common iEEG seizure onset pattern, see **Singh et al., 2015)**, CESS started more frequently with a FSD, even when they involved the same anatomical sites (Figure 1c,d); the way neural synchronization is produced could be therefore different in SS and CESS, although providing similar information about the spatial organisation of the EZ; iii) 30% of CESS and 43.5% of CS were elicited from a cortical region located outside the EZ, which can limit the utility of CESS for defining the extent of the resection; worse results were found by **Jacobs et al. (2010):** they found a maximum of 34% of stimulated contacts inducing an ictal response and located in the SOZ. On the other hand, interpretation may be less straightforward, and analysis of CESS must take into account the way the ictal discharge is generated, both spatially and temporally, rather than to simply consider that the seizure onset zone lies where the seizure is produced (**Trébuchon and Chauvel, 2016**); iv) 9/99 CESS were reported by the patients as non habitual, of which only 3 definitely showed unusual electro-clinical patterns after having reviewed the previously recorded episodes; the rate of such 'false positive' seizures therefore remains low (3%), but clinicians should be aware that such episodes do exist, especially in mesio-temporal lobe structures and when applying 50Hz CES; whether they are only a by-product of CES, or whether they need an abnormal underlying hyperexcitable cortex to be elicited remains debatable.

Can CES-elicited seizures contribute in improving surgical outcome ?

Despite a strong electro-clinical concordance between CESS and SS, the resections that included CESS-eliciting sites did not lead to any superior outcome, compared to resections that did not include these sites, as already showed in another study (**Schulz et al. 1997**).

CESS-eliciting sites, however, were fully resected in only a few patients of our series (4/24), so that the prognostic significance of removing CESS-eliciting sites cannot be definitely ruled out.

30 % of CESS and 43.5% of the CS were induced by a stimulation performed outside of the epileptogenic zone. This finding probably reflects the existence of cortical regions more extended than the considered epileptogenic zone which could participate in the seizure production. The limits of this region and the consequences of its resection on the post surgical prognostic were not evaluated. However, its lack of consideration could explain the recurrence of seizures after a transient post operative seizure-free period.

Finally, no association was found between the electroclinical correlations and the post operative outcome (neither electrical p=0.96 – nor clinical p=0.45). The epileptogenic zone appeared not to be better identified with a higher correlation rate. In our study, the small size of the sampling doesn't enable us to draw any conclusions. However, a high number of seizures was not associated to a worse prognostic, demonstrating that CESS do not disturb the presurgical evaluation and the cortical mapping, as it was assumed by Bank et al. **Bank et al (2014).**

THÈSE SOUTENUE PAR : Nastasia TARDY

TITRE :

Electro-clinical correlations of seizures induced by direct cortical stimulations and spontaneous seizures: relevance to define the epileptogenic zone.

CONCLUSION :

This study, even based on a small sampling, is the first one evaluating the electro-clinical correlations between spontaneous and stimulation-induced seizures and determining the relevance of the stimulations-induced discharges to define the epileptogenic zone.

Our results show a good overlap both for clinical and SEEG findings between the two types of seizures, therefore strongly suggesting that the epileptogenic network can be reactivated by the stimulation. This strengthens the usefulness of stimulation to delineate the epileptogenic zone. However, the removal of the brain area from which seizures were elicited did not seem to have any post-operative prognostic significance.

This study was based on visual analysis of SEEG signals, and further studies aiming at comparing spontaneous and electrically-induced seizures could benefit from quantitative measurements of SEEG signals, such as the epileptogenicity index (Bartholomei et al., 2008) or the epileptogenicity maps (David et al., 2011).

VU ET PERMIS D'IMPRIMER
Grenoble, le 20/10/2017

LE DOYEN
DE L'UFR DE MÉDECINE

Pour la Présidente
et par délégation
Le Doyen de Médecine
Pr. Jean-Paul ROMANET

Pr. Jean-Paul ROMANET

LE PRÉSIDENT DE LA THÈSE
JURY DE MÉDECINE

Pr. Philippe KAHANE

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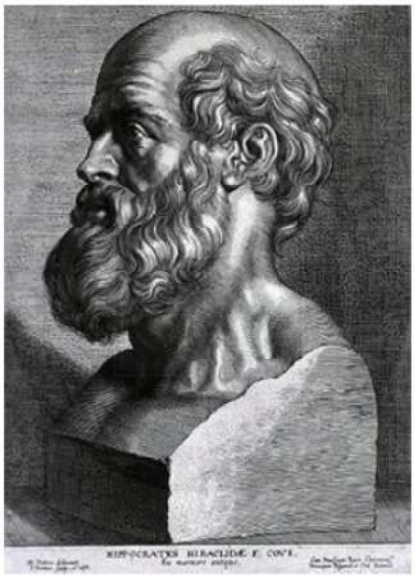
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

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Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

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