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Altered synchrony and loss of consciousness during frontal lobe seizures

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Abstract

Objective

Loss of consciousness (LOC) in frontal lobe epilepsy (FLE) has been rarely specifically studied until now. In this study we evaluated the LOC in a population of patients with FLE and studied the relationship between changes in synchrony and degree of LOC

Methods

24 patients undergoing stereoelectroencephalography (SEEG) during pre-surgical evaluation of FLE were studied. The LOC intensity was scored using the Consciousness Seizure Scale (CSS). For each studied seizure (n=52), interdependencies between signals recorded from 5 brain regions were estimated as a function of time by using non-linear regression analysis (h^2 coefficient).

Results

Seizures were divided into 3 groups according to the CSS scale: group A (no LOC) with a score ≤2, group B (intermediate or partial LOC) with a score ranging from 3 to 5, and group C (maximal LOC) with a score ≥ 6. The majority of seizures in FLE patients disclosed significant LOC, particularly for patients with prefrontal lobe seizures. Mean correlation values were significantly different between groups A and C ($p<0.001$), the maximal values of synchrony being observed in group C. Differences were significant for interaction affecting the external prefrontal cortex) ($p=0.004$) $p=0.01$) and the parietal cortex. In addition, a significant correlation was found between CSS scores and correlations values (h^2) of the prefrontal and the parietal region but not with the premotor cortex.

Conclusions:

This study indicates that in FLE, prefrontal seizures frequently alter consciousness. As in other focal seizures, LOC appears to be related to changes in synchrony in prefrontal and parietal associative cortices.

Significance: LOC in FLE is frequent and as in other focal epilepsies is related to an alteration of prefrontal-parietal network

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Keywords: Consciousness, Frontal cortex, Synchrony, Focal Epilepsy.

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Introduction

Loss of consciousness (LOC) is a serious clinical manifestation largely impacting the quality of life of patients with epilepsy (Cavanna and Monaco, 2009, Blumenfeld, 2011). A large body of evidence shows that LOC is associated with an increased risk of accidents and injury (Chen *et al.*, 2014). During the last ten years, there has been a marked increase in the amount of studies in this field. In particular, the mechanisms by which focal seizures may alter consciousness have been subject of investigations based on neuroimaging or neurophysiological approaches. Most of these studies have focused on temporal lobe epilepsy (TLE) (Gloor *et al.*, 1980, Munari *et al.*, 1980, Lux *et al.*, 2002, Blumenfeld *et al.*, 2004, Blumenfeld *et al.*, 2004, Arthuis *et al.*, 2009). It has been proposed that LOC in TLE is linked to an involvement of fronto-parietal cortices being inhibited (Blumenfeld *et al.*, 2004, Blumenfeld *et al.*, 2004) or abnormally over-synchronized (Arthuis *et al.*, 2009) during complex partial seizures. Associative parietal and frontal cortices have been largely demonstrated to be necessary for normal awareness and their alteration is associated with specific alteration of awareness without impacting arousal (Di Perri *et al.*, 2014).

A recent study from our group has stressed the role of parieto-frontal interaction in LOC associated with parietal seizures(Lambert *et al.*, 2012). Excessive EEG synchrony was correlated with the degree of consciousness alteration. Until now, no specific study has investigated the LOC in frontal lobe seizures. This study thus aimed at studying LOC in frontal lobe seizures and at investigating the relationship between changes in synchrony and degree of LOC during this kind of seizures. Given the role of the interactions between prefrontal regions and the parietal associative cortex in the “consciousness workspace” (Laureys *et al.*, 2005, Laureys *et al.*, 2007) we tested the hypothesis that consciousness

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alterations in frontal seizures are linked to prefrontal involvement and alterations of prefrontal-parietal synchronization.

Methods

Patients and SEEG recordings

24 patients undergoing pre-surgical evaluation of drug-resistant frontal lobe epilepsy (FLE) were selected from a series of patients in whom intracerebral recordings had been performed between 2001 and 2010 (Table 1). They were selected on the following basis: well defined frontal lobe seizures (epileptogenic zone well anatomically defined), at least one electrode explored the parietal lobe in addition with the frontal electrodes, and at least two seizures were useable for video analysis of LOC.

All patients underwent comprehensive evaluation including detailed history and neurological examination, neuropsychological testing, routine magnetic resonance imaging (MRI), surface electroencephalography (EEG) and stereoelectroencephalography (SEEG, depth electrodes). SEEG exploration was carried out during long-term video-EEG monitoring. Recordings were performed using intracerebral multiple contact electrodes (10 to 15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed according to Talairach's stereotactic method (Bartolomei *et al.*, 2011) as illustrated in figure 1.

The anatomical targeting of electrodes was established in each patient according to available non-invasive information and hypotheses about the localization of the epileptogenic zone (for details see previous reports (Bartolomei *et al.*, 2011). CT-scan/MRI data fusion was performed to accurately check the anatomical location of each contact along the electrode trajectory using MEDINRIA software (http://gforge.inria.fr/projects/medinria). In selected

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patients, several distinct functional regions of the frontal lobe were explored (Fig. 1). In the selected cases, electrodes sampling extrafrontal regions were also available. Signals were recorded on a 128 channel Deltamed/NATUS^{TM} system. They were sampled at 512 Hz and recorded on a hard disk (16 bits/sample) using no digital filter. A high-pass filter (cut-off frequency equal to 0.16 Hz at -3 dB) was used to remove very slow variations that sometimes contaminate the baseline. Table 1 provides clinical information about the patients selected for the purpose of this study.

Determination of LOC during seizures: the consciousness seizure scale (CSS)

One to three representative seizures from each patient were analyzed. Video stereotactic-EEG (SEEG) recordings were reviewed and LOC intensity was scored by two of the authors (FBo and IL, blinded to the EEG signal analysis) using an eight criteria scale (Consciousness Seizure Scale, CSS, Arthuis *et al.*, 2009). This scale is detailed in the "Supplementary method" and has been validated in term of inter-rater reproductibility in our seminal paper (Arthuis *et al.*, 2009). The mean of the two scores was retained for each analyzed seizure. Each seizure has been scored from 0 (no alteration of consciousness) to 9 (complete alteration of consciousness). This scale can be used provided that a good interaction and examination of the patient was performed during seizure. A standardized protocol assessing patients' responsiveness is used during video EEG recordings in our epilepsy unit (see the "Supplementary method"). Finally 52 video recorded seizures from those 24 patients were retained for analysis.

SEEG signal analysis

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Definition of regions of interest:

In this study, we specifically analyzed the relationship between bipolar intracerebral EEG signals (derived from two contiguous leads of the same electrode) recorded from regions of interest. These regions could be variable from one patient to the other but included at least prefrontal cortices (internal and external part) and parietal regions (internal and external part). Internal part of prefrontal cortex refers to the internal contacts of prefrontal electrodes reaching the cingulate gyrus or the supra-cingulate regions. External part refers to the lateral contacts of the electrodes exploring the dorsolateral prefrontal cortex (see example in Fig 1). For each patient we chose bipolar derivations representative of at least two prefrontal regions, two parietal sub-regions and one premotor or motor region. Signal correlation ("synchronization") was evaluated between SEEG signals recorded from these selected regions. Therefore the estimation of correlations involved both intralobar synchronization (for interactions in the frontal lobe) and long distance interlobar synchronization (parieto-temporal, fronto-temporal or parieto-frontal interactions).

Periods of interest:

In order to compare the 52 seizures previously selected, two periods of interest were defined reflecting the neural activity during the seizure as compared to a background one.

-Background (BKG): this period of 30 seconds was selected at least 1 min apart from the onset of the ictal discharge, during a period of awake quiet rest and of normal consciousness state. When the seizure was elicited by electrical stimulation, the BKG period was selected one minute before the onset of the first stimulation.

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-Seizure period (SP): This period was defined as the period starting from the onset of the rapid discharge to the end of the SEEG discharges.

Estimation of long-distance synchronization during seizures

The synchronization of EEG signals between two distant regions may be estimated by several different methods (Stam, 2005, Ansari-Asl *et al.*, 2006) aimed at evaluating the degree of mathematical relationship between signals. In the present paper, interdependencies between signals recorded from 5 regions were estimated as a function of time by using non-linear regression analysis (Pijn and Lopes Da Silva, 1993). Details of the method can be found in our previous studies (Bartolomei *et al.*, 2004, Guye *et al.*, 2006, Arthuis *et al.*, 2009). 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. In contrast, 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. The analysis was performed over a sliding window (duration: 3 s) by steps of 0.25 s. The h^2 values were averaged over the two periods of interest defined above, for each of the considered pairs of signals (see below) and for each of the 52 seizures recordings. We particularly chose to study the values obtained between each individual bipolar derivation representative of one brain region and all the other selected bipolar channels.

In the present study, h^2 values were computed on broadband signals (0.5-90 hz), providing a global estimation of nonlinear interdependencies. A total of 10 interactions (5 brain regions) were estimated in each studied seizure.

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Statistical analysis

For each seizure, the correlation values computed from ictal period were normalized with respect to the value obtained in the background period using a Z-score transformation. These values will be denoted by Zh^2 in the following. This value indicates, for each interaction, the change in signal synchronization relative to the background period. As the data were not normally distributed, a non-parametric Mann–Whitney test was used to estimate whether Zh^2 values were different between two different groups of seizures defined with the CSS: one with no alteration of consciousness (Group A) and one with profound alteration of consciousness (Group C). Since we analysed the averaged Zh^2 values from 5 regions, a Bonferroni correction was applied. Therefore a p value <0.01 was considered significant.
A Spearman correlation test was applied to correlate the Zh^2 values obtained in the different selected regions and the CSS scores. A $p <0.05$ was considered significant.

Results

A summary of clinical data obtained in the 24 patients is provided in Table 1.

Alteration of Consciousness in frontal seizures:

Seizures were divided into 3 groups according to the consciousness alteration scored using the CSS scale: group A (no LOC) with a score ≤ 2, group B (intermediate or partial LOC) with a score ranging from 2 to 5, and group C (maximal LOC) with a score ≥ 6.

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Group A included 15 seizures, group B 9 seizures and group C 28 seizures. All seizures occurred spontaneously except 4 seizures in three patients that were triggered by electrical stimulation. Spontaneous and triggered seizures were classified in the same group for these patients (see the Supplementary Table S1). Therefore the majority of seizures in patients with frontal seizures disclosed LOC (28/52, %, group C, 9/52 Group B). These three groups are represented in figure 2A. Interestingly, the distribution of the groups was different within the different forms of frontal lobe seizures. Seizures with maximal LOC (group C) were observed essentially in prefrontal or prefronto-temporal seizures while seizures with minimal LOC (Group A) were observed in motor and premotor seizures. Taken as a whole, prefrontal/prefronto-temporal seizures always altered consciousness (groups B and C) in contrast with premotor/motor seizures in which the LOC was absent in 15/22 (68%) seizures (Fig. 2B).

Relationship between altered consciousness and synchronization changes

We first looked for differences in the values of averaged interactions between the 5 regions (representing 10 interactions: prefrontal internal and external (PFi, PFe); parietal internal and external (PAi; PAe); premotor or motor region (PreM)) between group A (with no LOC) and group C (maximal LOC). Interactions were estimated using Z-scores of h^2 values (Zh^2) obtained in each bipolar signal derived from selected regions.

Figure 2C shows the averaged values of Zh^2 for all the interactions in two seizures groups with maximal (group C) or minimal (group A) loss of consciousness. Values were significantly different between the two groups ($p<0.001$, Mann–Whitney), the maximal values of synchrony (Zh^2) being observed in group C. We did not find differences between group B and C values ($p=0.43$, Mann–Whitney) and between groups B and A

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(p=0.71, Mann–Whitney). This may be due to the low number of seizures in this group (n=9) and the fact that group B seizures disclosed intermediary values between group A and C.

Examples of two different seizures disclosing different values of LOC are depicted in Figure 1B. As illustrated, pattern of synchrony was different in the two seizures, with maximal synchrony level (Zh^2) and distribution observed in group C seizures.

These results are in favour of a more important change in synchrony in the cortical networks affected by seizure activity in the group of seizures with the maximal LOC in comparison with the group with no LOC.

Relation between correlations values in different anatomical regions and consciousness

We then investigated whether CSS scores were differently correlated with values averaged for h^2Zscores values affecting the 5 brain regions of interest. To this aim, we have computed the average synchronization (h^2) between each channel belonging to a given region ((PFi; PFe; PAi, PAe, PM) and secondarily determined the Zscores values. Then, Zh^2 values were compared between group A and group C seizures. Figure 2D show the obtained mean Zh^2 values in the five regions. As expected, values in group C seizures were found to be superior to those in groupA seizures, but differences were significant only for interaction affecting the regions PFe (external prefrontal cortex, p=0.004), PAe (external parietal cortex, p=0.01). We observed a trend for PAi (internal parietal cortex, p=0.02) and differences were not significant for PFi (prefrontal internal, p=0.13) and PM (premotor cortex, p=0.09).

We then looked at the relationship between Zh^2 values in PFi, PAi and PAe and consciousness scores. These relations are shown in figure 1C, and appear to be non-linear. Spearman test shows a significant correlation between values of the prefrontal region (PFi, p=0.04; PFe,

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p=0.002) and the parietal region (PAi, p=0.007; PAe, p=0.01) but not with the premotor cortex (p=0.06).

Discussion

Following our previous studies in other localizations (Arthuis *et al.*, 2009, Lambert *et al.*, 2012), we investigated the role of “synchronization” changes in frontal lobe seizures.
We found that seizures affecting the prefrontal cortex were more often associated with LOC than the other main type of FLS, the premotor or/and motor seizures. This result was obtained through a quantification of the consciousness alteration using the Consciousness Seizure Scale (Arthuis *et al.*, 2009), showing that most of the prefrontal seizures deeply alter consciousness. In contrast, only a minority of premotor/motor seizures (31%) are accompanied by an alteration of consciousness. This is in keeping with previous observations that motor cortex appears not to be functionally affected during altered consciousness (Bancaud and Talairach, 1992, Blumenfeld *et al.*, 2004).
This is also in agreement with the role of prefrontal cortex in the processing of consciousness. Numerous studies have reported that the alteration of prefrontal/parietal areas is a core aspect of disorders producing altered consciousness (Laureys *et al.*, 1999, Di Perri *et al.*, 2014). These areas support the long distance connectivity and re-entrant loops constituting a “global workspace” of consciousness (review in (Dehaene and Naccache, 2001, Rees *et al.*, 2002, Dehaene and Changeux, 2011). External consciousness representations are probably more dependent on the lateral part of these cortices while internal/self consciousness is more correlated with the medial part of the prefrontal and parietal regions (Laureys *et al.*, 2005, Laureys *et al.*, 2007).

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In FLS, we found that these two awareness networks are affected by seizure activity. The link of excess synchronization in these regions and LOC was further demonstrated by the significant relationship between the level of consciousness alteration and the level of synchrony. The curve of the relationship between altered synchronization and consciousness alteration is suggestive of a non-linear process. It appears that above a certain value of synchrony, most of the patients have marked loss of consciousness.

These results are thus close to those we found in temporal lobe seizures (Arthuis *et al.*, 2009, Bartolomei and Naccache, 2011) and in parietal seizures (Lambert *et al.*, 2012).

Despite great differences in the clinical expression of these different types of seizures, they advocate for a common mechanism of the awareness alterations in focal seizures. In particular, the same relationship between synchronization values in parieto-frontal regions and the degree of LOC suggest that the maintenance of contact/awareness in seizure is dependent on the level of synchronization in the same associative regions.

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Conflict of Interest

None of the authors has any conflict of interest to disclose.

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Legends of Table and Figures

Table 1. General characteristics of patient population.

Abbreviations: M: male; F: female; FCD: focal cortical dysplasia; R: right, L: left; preF: pre-frontal; preM: pre-motor; preC: pre-central.

Figure 1.

A) Upper part: SEEG recordings of a frontal seizure (P12, GrA seizure with no loss of consciousness). On the right: SEEG scheme on a lateral view of all depth electrodes superimposed on a 3D reconstruction of the neocortical surface of the brain. Seven intracerebral multiple contact electrodes denoted by letters CR, CC, PM, SA, OF, CS, PA. The electrodes CC and SA are located in the premotor cortices (Area 6 lateral and SMA in the internal contacts for electrode SA, cingulate motor area for electrode Cc, yellow circles). Electrode CS is a trans-rolandic electrode recording the pre and post-central sulci. Electrode PA is in the superior parietal region (red circle). The electrodes PM and CR explore the prefrontal cortex (orange circles) and the electrode Of the opercular cortex. On the left part: Each line corresponds to a bipolar recording between two adjacent contacts of the electrode and representative of a brain region PFi: internal prefrontal cortex (internal contact electrode CR; PM: premotor cortex: internal contacts of electrode SA; PFe: lateral prefrontal cortex, lateral contacts of electrode CR; PAi: parietal internal, internal contacts of electrode PA; and PAe: external regions, lateral contacts of electrode PA. Seizure starts from the premotor cortex and affect the parietal region.

Lower part: Bivariate estimation of cross correlations (computation of the h^2 non linear correlation) between the 5 selected traces.

B) Example of correlations changes in two examples of seizures, a group A seizure and a group C seizure. Figure represents graphs of correlation and synchronization matrices. The synchronization matrix is a 5 x 5 square matrix, where the x axis and the y axis correspond with the channel numbers (each representing one brain region), and where

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the entries indicate the mean strength of the h^2 between specific pairs of channels. The strength of the h^2 is indicated with a colour scale, from blue ($h^2 = 0$) to red ($h^2 = 1$). The diagonal running from the upper left to the lower right is intentionally left red. Slight differences can be observed along the diagonal because of the asymmetrical nature of the nonlinear correlation coefficient h^2 (values of the h^2 coefficient are different when the computation is performed from signal X to signal Y versus Y to X). The graphs of correlations represent the mean values of h_{xy}^2 and h_{yx}^2 and are thresholded with the same value (0.1) for each case. Only link with values above this threshold are represented. More links and links with increased values are observed in the group C seizure with regard to the group A seizure.

C) Graph showing the relationship between between Zh^2 values and CSS scores for interactions affecting the Prefrontal internal and external regions (PFi; PFe) the parietal internal and external regions (PAi; PAe) and the premotor/motor region (PreM).

Figure 2.

A) Distribution of the consciousness scores using the CSS scores according to the three defined groups of seizures (A, B, C).

B) Distribution of the consciousness scores according to the three defined groups of seizures (A, B, C) and the type of frontal seizures: PF: prefrontal, PF+T: prefronto-temporal; PM/M: premotor/motor

C) Figure shows the averaged values of Z-Scores values of h^2 for all the interactions in two seizures groups with maximal (group C) or minimal (group A) loss of consciousness. Values are higher in group C than in group A.

D) Zh^2 values for interactions affecting the Prefrontal internal and external regions (PFi; PFe) the parietal internal and external regions (PAi; PAe) and the premotor or motor region (PreM). Group C seizures disclosed higher values than group A seizures, significant for PFe ($p=0.004$), PAe ($p=0.01$) and PAi ($p=0.02$).

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Figure 1

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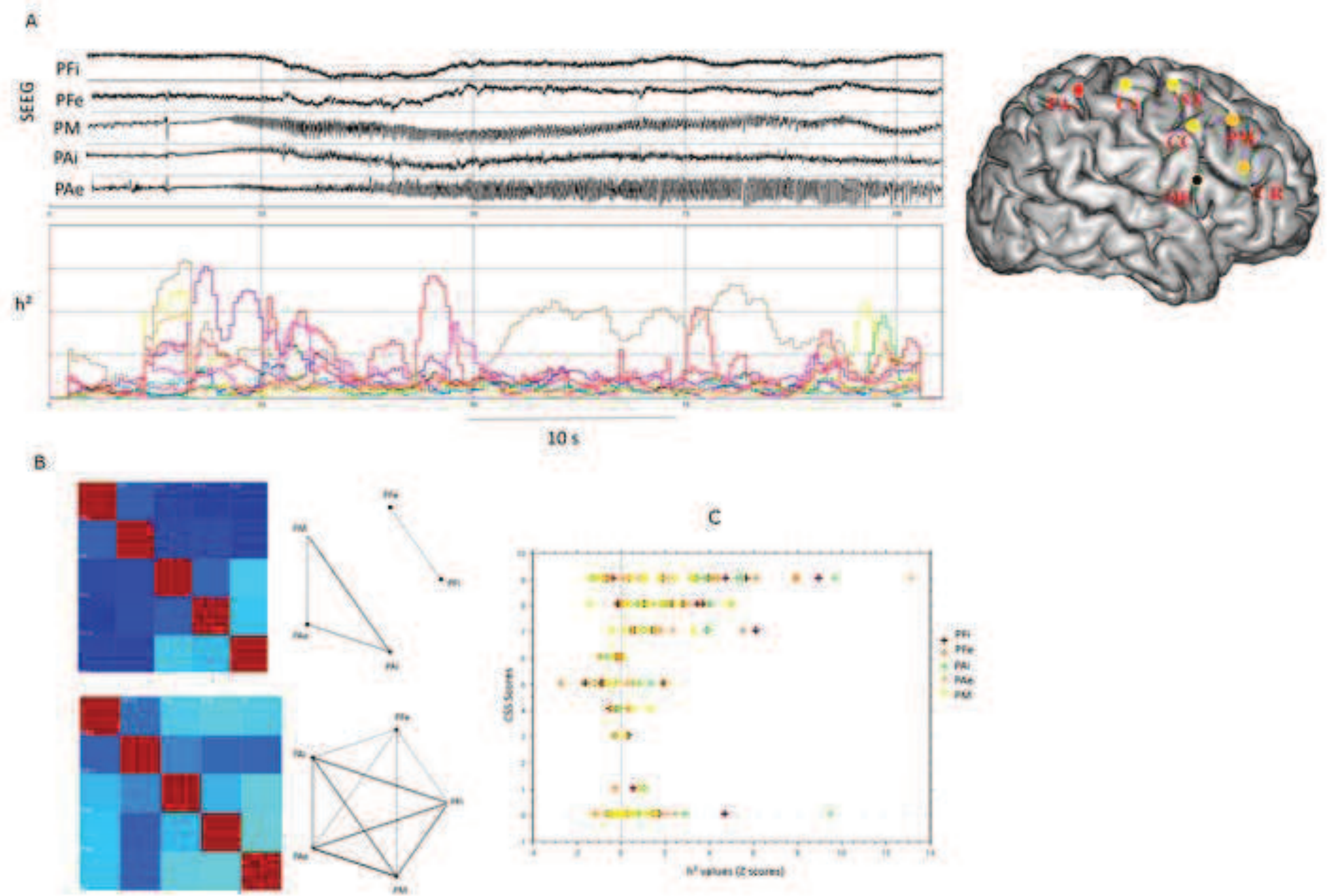

Figure 2

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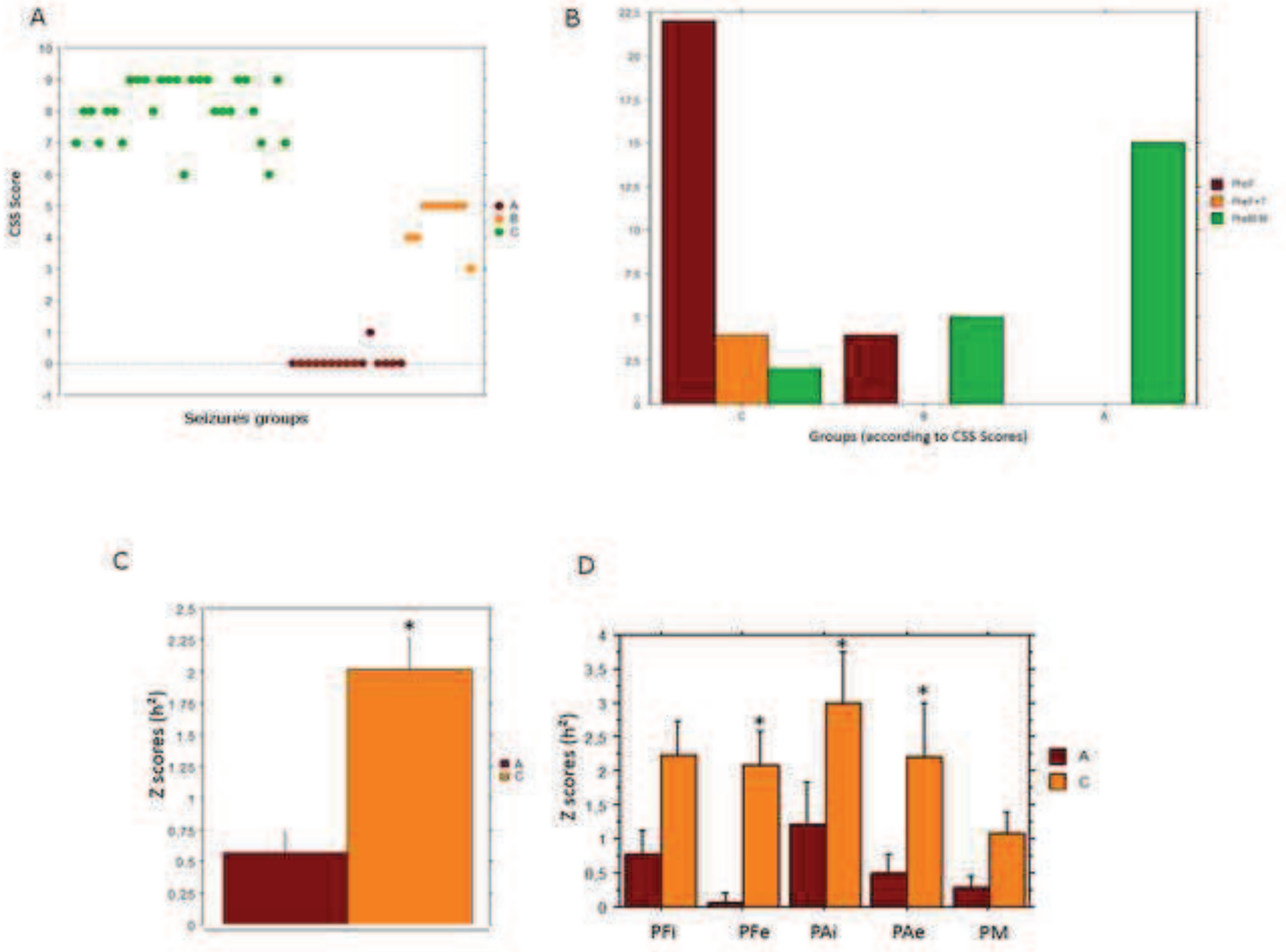

Table 1

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_	Sex	Age at onset (y)	Age at recordings (y)	Epilepsy side	MRI/aetiology	Surgery	ILAE Class	Follow up (y)	EZ
P1	F	17	47	L	Post-infective lesion	Refused			preF
P2	F	4	32	L	Surgical scar	Radiosurgery	2	4	preC
P3	F	4	19	L	FCD	Yes	1	8	preF
P4	F	12	34	L	FCD	Yes	1	4	preF
P5	F	8	22	R	Herpetic encephalitis	Yes	3	2	preF+T
P6	M	9	11	R	FCD	Yes	1	1,5	preM
P7	M	6	30	R	Cryptogenic	Yes	1	10	preF+T
P8	M	13	38	R	Cryptogenic	Refused			preC/preM
P9	M	17	32	R	Cryptogenic	Contraindicated			preF bilateral
P10	F	3	24	L	FCD	Yes	4	9	preM
P11	F	1	14	R	FCD	Awaited			preC/preM
P12	M	12	29	R	FCD	Yes	5	2	preM
P13	F	11	25	R	Cryptogenic	Radiosurgery	4	4	preC
P14	M	17	20	Bilateral	Cryptogenic	Callosotomy	5	6	preF
P15	F	6	22	R	Cryptogenic	Contraindicated			preF
P16	M	1	8	R	FCD	Yes	1	9	preF
P17	F	18	26	L	Post-traumatic	Yes	1	1	preF
P18	M	16	33	R	FCD	Yes	1	9	preF
P19	M	12	30	L	Cerebral abscess	Yes	1	8	preF
P20	M	5	29	R	Cryptogenic	Refused			preF
P21	F	4	12	L	FCD	Yes	1	6	preM
P22	M	1	34	R	Cavernoma	Radiosurgery	2	2	preF
P23	F	3	19	L	Cryptogenic	Contraindicated			preM/preF
P24	F	1	8	R	Cryptogenic	Yes	2	3	preC

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Highlights

1. This study investigated loss of consciousness in 52 frontal seizures.

2. Interdependencies between signals were estimated by using non-linear regression analysis.

3. Loss of consciousness appears to be related to changes in synchrony in prefrontal and parietal associative cortices.

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