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BRIEF COMMUNICATION

Localization of Epileptogenic Zone on Pre-surgical Intracranial EEG Recordings: Toward a Validation of Quantitative Signal Analysis Approaches

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Abstract In patients diagnosed with pharmaco-resistant epilepsy, cerebral areas responsible for seizure generation can be defined by performing implantation of intracranial electrodes. The identification of the epileptogenic zone (EZ) is based on visual inspection of the intracranial electroencephalogram (IEEG) performed by highly qualified neurophysiologists. New computer-based quantitative EEG analyses have been developed in collaboration with the signal analysis community to expedite EZ detection. The aim of the present report is to compare different signal analysis approaches developed in four different European laboratories working in close collaboration with four European Epilepsy Centers. Computer-based signal analysis methods were retrospectively applied to IEEG recordings performed in four patients undergoing pre-surgical exploration of pharmaco-resistant epilepsy. The four methods elaborated by the different teams to identify the EZ are based either on frequency analysis, on nonlinear signal analysis, on connectivity measures or on statistical parametric mapping of epileptogenicity indices. All methods converge on the identification of EZ in patients that present with fast activity at seizure onset. When traditional visual inspection was not successful in detecting EZ on IEEG, the different signal analysis methods produced highly discordant results. Quantitative analysis of IEEG recordings complement clinical evaluation by contributing to the study of epileptogenic networks during seizures. We demonstrate that the degree of sensitivity of different computer-based methods to detect the EZ in respect to visual EEG inspection depends on the specific seizure pattern.

Keywords Computer-based signal analysis · Epilepsy surgery · Epileptogenic zone · Focal epilepsy · Intracranial EEG

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Abbreviations

EI	Epileptogenicity Index
EZ	Epileptogenic zone
FCD	Focal cortical dysplasia
IEEG	Intracranial electroencephalogram
NLSI	Nonlinear Structure Index
QFAI	Quantified Frequency Analysis Index
SEEG	Stereo electroencephalogram
SPMEI	Statistical Parametric Mapping of Epileptogenicity Index

Introduction

In patients suffering from drug-resistant focal seizures candidate to epilepsy surgery, the identification of the cortical areas to be removed to cure the patients requires intracranial EEG (IEEG) recordings with either subdural or depth electrodes in 25–50 % of the cases (Talairach et al. 1974; Kahane et al. 2003; Cossu et al. 2005; Kahane and Spencer 2012; Yuan et al. 2012; Cardinale et al. 2013; Gonzalez-Martinez et al. 2013). Boundaries of the epileptogenic zone (EZ), defined as the area of cortex involved in seizures generation, are defined by visually reviewing IEEG signals during seizures and the interictal state. Since intracerebral recordings are performed with many electrode contacts (up to 200) positioned in pre-selected brain regions for several days, a time-consuming reviewing process by highly qualified and trained neurophysiologists is required.

In a subset of patients, estimation of EZ is difficult even after intracranial exploration partly because of the complex spatial distribution of ictal electrographic patterns. A faster and more quantitative approach to study the EZ may improve the visual inspection of IEEG signals. Novel signal analysis approaches to identify the EZ have been developed by close collaborations between clinical neurophysiologists and researchers in signal processing. Compared to visual inspection, quantitative analysis of intracranial signals is expected to (i) expedite EZ detection, (ii) provide precise and objective results, (iii) reduce the bias due to the operator and (iv) improve understanding of EEG patterns in the EZ and in the surrounding areas. As an additional value, the use of quantitative methods developed in signal analysis and neurobiological concepts will help to understand focal ictogenesis and the pathophysiology of involved epileptogenic networks.

The aim of the present report is to apply four quantitative methods developed at four European Epilepsy Centers to EEG signals recorded from patients explored with intracranial electrodes and to validate the computational approach to EZ detection. Details on the different methods were described in details in previous reports (Bartolomei et al. 2008; David et al. 2011; Gnatkovsky et al. 2011; Andrzejak et al. 2012). Epileptogenicity indices and their mapping have been utilized to identify seizure networks in temporal and temporal "plus" epilepsy (Bartolomei et al. 2008; Aubert et al. 2009; Blauwblomme et al. 2013) and in frontal and occipital areas (Bartolomei et al. 2011; David et al. 2011). The intra-method reproducibility of seizure patterns and networks within the same patient has also been studied (David et al. 2011; Gnatkovsky et al. 2011). Analysis of long-term IEEG recordings of the seizure-free interval demonstrated that so-called surrogate-baseline corrected nonlinear signal analysis measures allowed to determine the seizure-generating hemispheres in patients with mesio-temporal lobe epilepsy (Andrzejak et al. 2001, 2011).

In order to compare results, the four methods (see details in the supplementary material) were retrospectively applied on the same set of intracranial EEG data recorded from four patients that represent different clinical conditions submitted to pre-surgical monitoring.

Results

Four patients with IEEG illustrative of the most common focal seizure patterns were retrospectively selected. Pt1, Pt2 and Pt3 were recorded with depth electrodes whereas Pt4 was explored with subdural strips and *foramen ovale* electrodes. The results of visual evaluation of the IEEG are shown in Table 1. Pts1, 2 and 4 were operated on to remove the EZ identified with the traditional visual analysis method with an excellent post-surgical neurological and seizure outcome (class I, evaluated at 2 years and confirmed at present follow-up; Table 1). EZ could not be detected in Pt3 and the patient was excluded from surgical planning. The results of traditional visual analysis is represented in Fig. 1 by red-filled rectangles in each panel and marked by red spheres in the 3D brain scheme. The results of computer-based signal analysis to localize the EZ performed with the four methods (QFAI, SPMEI, NLSI and EI, see supplementary material) are illustrated for each patient (Fig. 1). The four indexes were calculated and averaged for each recording site. In Pt1, Pt2 and Pt4, high index values were observed in electrodes included in the EZ identified by traditional visual analysis. In these patients, different methods revealed high index values also in regions that were not identified as EZ by visual analysis. All methods exhibit high index values for visually identified EZ in Pt1 and Pt2. For these two patients, QFAI method was most specific, while EI, SPMEI and NLSI methods identified additional high index values on

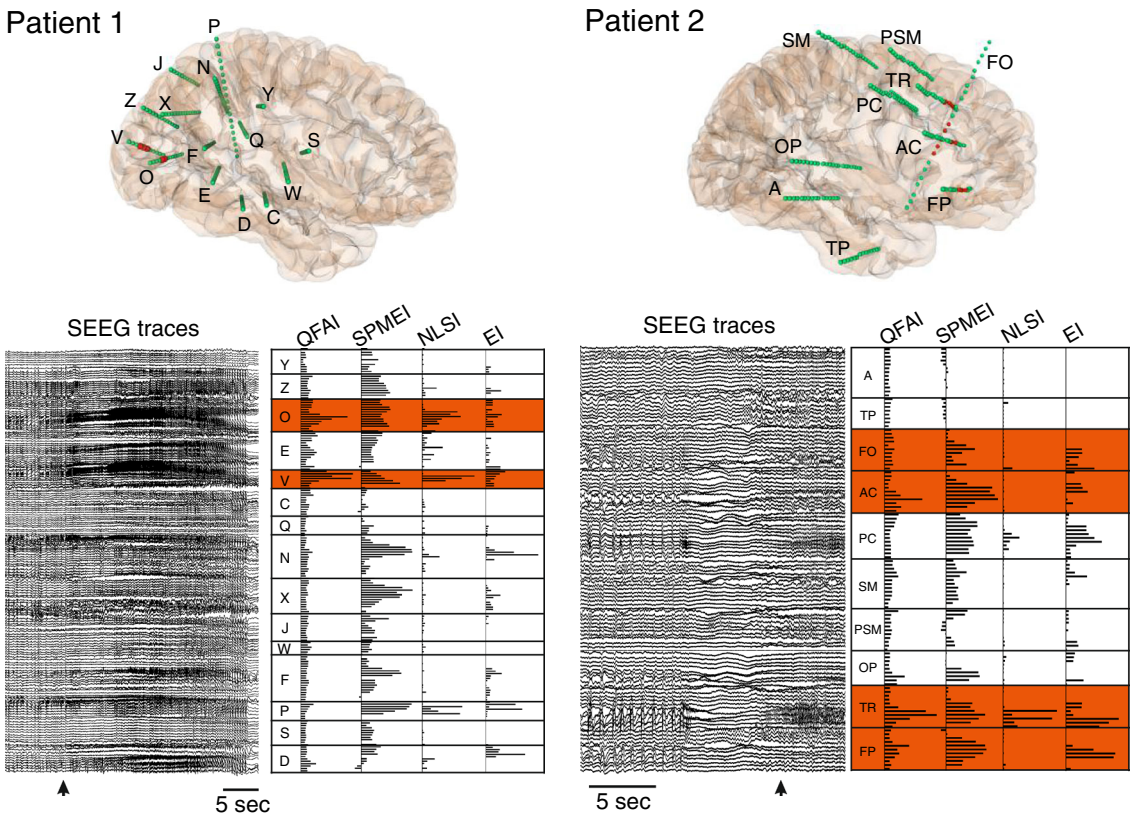
Table 1 Clinical, imaging and post-surgical outcome data for the four patients included in the study

	Age (years)	Gender	Age at 1st seizure (years)	MRI	Functional imaging	n. IEEG-recorded seizures	EZ detection by visual inspection	Age at surgery (years)	Histologic diagnosis	Engel scale
Pt 1	19	F	6	FCD	No	11	R temporo-occipital	17	R temporo-occipital FCD Taylor IIb	IA
Pt 2	43	M	16	negative	R frontal abnormal.	3	R Frontal	33	R frontal FCD Taylor IIB	IA
Pt 3	28	F	10	negative	SPECT: R hemisphere hypocapt	1	Not achieved	No surger	cryptogenic	–
Pt 4	24	M	4	R hippocampal and hemisphere atrophy	No	5	R temporo-polar, mesio-temporal	18	R hippocampal sclerosis	IA

electrodes N, X, F and P in Pt1, as well as PC and OP electrodes in Pt2. Good agreement among EI, NLSI and QFAI methods was observed for the identification of the TAR strip electrode in the EZ of Pt4. EI method could identify a second set of sites on the right *foramen ovale* electrode (FOR). The evaluation of seizure discharges in Pt3 generated highly discordant localizing data with both traditional and computer-based signal analysis techniques.

Discussion

The only aim of the study is to compare different computer-based methods developed by teams that have an extensive and routinary use of diagnostic IEEG in epilepsy patients. The main goal of this manuscript is to report, for the first time, the results from the qualitative comparison (i.e. without a strict cross-validation on large datasets) of methods that are detailed already in previous published papers (see Methods). The present study compares the findings obtained by applying different computer-based signal analysis methods to detect the EZ in patients with focal pharmacoresistant epilepsies explored with intracranial electrodes. The patients were selected as representative cases that illustrate the most frequent typical IEEG patterns observed during pre-surgical monitoring of focal drug-resistant epilepsies. Reports on the validation of individual methods that utilize larger patient cohorts have been previously published (Andrzejak et al. 2001; Bartolomei et al. 2008; David et al. 2011; Gnatkovsky et al. 2011; Andrzejak et al. 2012; Gnatkovsky et al. 2014). In this study, the four different approaches were compared on the same set of IEEG data obtained from patients that represent paradigmatic clinical conditions selected for IEEG exploration. The EZ indices reported here represent contacts/networks involved during the seizure as a whole. Fragments of seizure (pre-ictal period, seizure onset, seizure termination, etc.) were not considered in the present comparison, but can be potentially analyzed, according to the question and hypothesis that is considered (Osorio et al. 2011). The focus on specific time points of a seizure was not considered either and can potentially influence the specificity of the different methods. The decision to analyze EZ networks on the entire seizure discharge can explain the different spatial specificity observed by comparing the four methods. It is worth noting that such a multi-center comparison of EZ detection methods was never performed before. Pt1 and Pt2 exemplified FCD cases characterized by low-voltage fast activity at seizure onset identified with the SEEG electrodes (Tassi et al. 2002; Francione et al. 2003), with (Pt1) and without (Pt2) an obvious lesion on the MRI. Pt4 presented with a hippocampal sclerosis associated with hemispheric atrophy and diffuse EEG abnormalities. Pt3


Patient 1
P
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SEEG traces
QFAI
SPMEI
NLSI
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Patient 2
SM
PSM
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TR
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A
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SEEG traces
QFAI
SPMEI
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PSM
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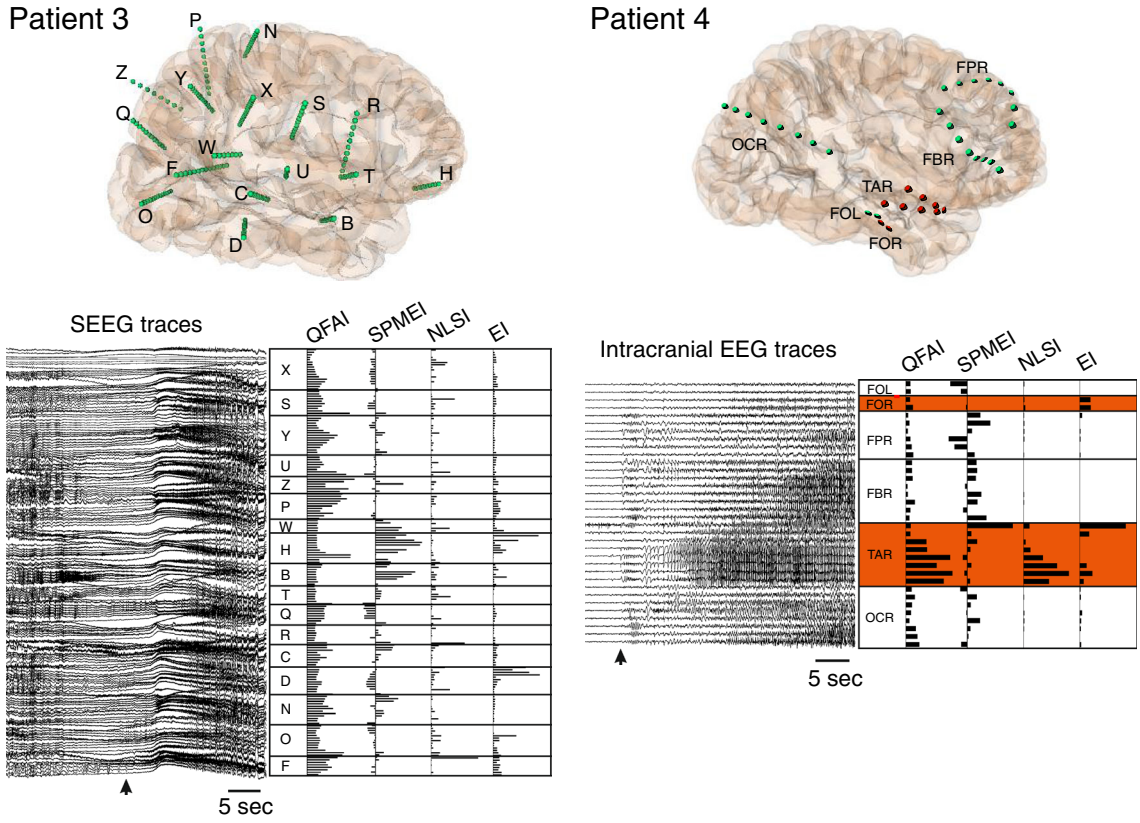
Patient 3
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SEEG traces
QFAI
SPMEI
NLSI
EI
X
S
Y
U
Z
P
W
H
B
T
Q
R
C
D
N
O
F
5 sec
Patient 4
FPR
OCR
FBR
TAR
FOL
FOR
Intracranial EEG traces
QFAI
SPMEI
NLSI
EI
FOL
FOR
FPR
FBR
TAR
OCR
5 sec

◀**Fig. 1** Electrode positions on 3D brain schemes (*top* in each *panel*), IEEG recordings (*left bottom* in each *panel*) and mean values of indices obtained with the four different methods (*right bottom*; QFAI, SPMEI, NLSI and EI) applied to patients 1–4. The EZ identified by traditional visual analysis (and surgically removed) is represented by *red rectangles* next to the contact names and are marked by *red spheres* in the 3D brain scheme. The amplitude of the *horizontal bars* in the analysis graph illustrate the relative value of the specific index for each trace represented on the IEEG. Seizure onsets are marked by the *arrows* (Color figure online)

was MRI negative, and showed diffuse activation at seizure onset and was excluded from epilepsy surgery because a clear EZ could not be delineated by traditional visual analysis. The apparent lack of convergence between results obtained with different methods in some patients might also indicate that the EZ can be better conceptualized as a network structure with different nodes ("hubs"). Each node might manifest itself by distinct IEEG feature, for which different methods probably have different sensitivities and specificities. Only taking the information of all measures, one might characterize the full network. The removal of any of the nodes might potentially lead to seizure freedom. Thus, the definition of the EZ as the region that has to be removed as a whole to abolish seizures may not apply to all patients (Rosenow and Lüders 2001).

The study demonstrates that computer-based signal analysis methods can provide useful information for the localization of the EZ. Our findings support the concept that different parameters related to the intrinsic content of IEEG signals are effective in detecting the EZ, independent off the specific algorithm that was applied to calculate seizure indices. The methods quantify different aspects of neurophysiological signals and can therefore provide quantified information which can complement each other and complement the classical clinical analysis. Each method has its own specific properties. EI and QFAI are semi-automatic and rely on the detection of the seizure onset period defined by the clinical neurophysiologist. Both methods are based on the identification of fast activities and, as expected, were efficient in localizing the EZ in those patients that presented with low-voltage fast activity during seizure, such as Pt1 and Pt2. SPMEI method is fully-automatic and is based on statistical parametric mapping (SPM) of the EI in a frequency band of interest selected a priori. Statistics are produced according to a period of reference during the interictal state. This reference period, which is only used by this method, may also explain some differences of epileptogenicity values sometimes observed with those of the other methods. Overall, SPMEI produced the largest ictal "activations" because of this normalisation step and because of the spatial smoothing required for the correction of multiple comparisons within the SPMs. Unlike other methods focused on the ictal discharge, NLSI evaluation is based on the automated analysis of long periods of seizure-free EEG recordings.

Our results encourage a computerized approach in patients that present with prominent fast activity at seizure onset. Computer-based signal analysis of IEEG in these patients is faster and less critically dependent on the experience of the referee, and may help to identify reproducible or varying network patterns during successive seizures recorded in the same patient (David et al. 2011; Gnatkovsky et al. 2011). Interestingly, the fully-automatic NLSI analysis of the interictal period in our patients indicated an EZ that highly overlapped with the results of the analysis of seizure patterns performed with the other methods. This result confirms that interictal periods also convey valuable information on the epileptogenic brain tissue, at least in some patients. It also confirms that all methods are effective in locating the EZ, independent on both the EEG epoch that was evaluated and the property of the neurophysiological signal considered by the signal analysis algorithm. This is a crucial finding that supports the inter-method comparability.

None of the signal analysis methods provides results that strictly match the clinical identification of epileptogenic sites. In most cases, methods identify more epileptogenic regions than clinicians did. This implies that while the methods have a good sensitivity they may have a limited specificity. On the other hand, different methods often converged in pointing to the same electrode contacts located outside the EZ defined by the clinicians. More specifically, EI and SPMEI methods identified additional recording sites on electrodes positioned in close proximity to the visually-detected EZ electrodes E, N, X, F and P for Pt1 as well as PC and OP for Pt2. Sites on electrodes P and N in Pt1 as well as on electrode PC in Pt2 had also high NLSI values. Distal OP recording sites showed high QFAI in the same patient. This may suggest that IEEG signal features that remain sub-threshold to visual inspection can be revealed by quantitative analysis and the actual EZ can be larger than the one detected by visual inspection. In this case, the excellent seizure outcome observed in these patients suggests that, at least in FCD patients Pt1 and Pt2, a partial removal of the epileptogenic network can successfully stop seizures. FCD is a good example in which analysis of seizure patterns is possibly more efficient than interictal data evaluation (Tassi et al. 2002). SPMEI in such case is possibly less efficient in detecting the EZ because the baseline period has high fractions of fast activities in the region from where seizures start.

Patient 3 was considered as a very difficult case by epileptologists who decided to not operate this patient given the complexity of the seizure onset pattern and the wide extent of the ictal activity. Also our quantitative signal analysis did not allow for a clear definition of the EZ in this patient. No congruent findings across the different

methods were observed. This agreement with regard to the lack of a clear EZ can be explained by the fact that three of the four methods are based on the detection of EEG signal components that are evident on visual inspection, such as fast activity and very slow polarizing potentials.

Computer-based evaluation of IEEG with different signal analysis methods demonstrates a good sensitivity for EZ detection. The comparison of different methods confirmed a convergence of findings. Computer-based analysis of IEEG can be valuable to characterize epileptogenic networks and to quantify reproducibility of seizure patterns.

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

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