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Detection of recurrent activation patterns across focal seizures: Application to seizure onset zone identification

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HIGHLIGHTS

- Consistent recurrent seizures allow to estimate channel activation patterns delineating the seizure onset zone (SOZ).
- The SOZ is characterized by low activation onset times and large time-average activation values.
- SOZ discrimination is maximized below the gamma band when the entire seizure period is considered.

ABSTRACT

Objective: We introduce a method that quantifies the consistent involvement of intracranially monitored regions in recurrent focal seizures.
Methods: We evaluated the consistency of two ictal spectral activation patterns (mean power change and power change onset time) in intracranial recordings across focal seizures from seven patients with clinically marked seizure onset zone (SOZ). We examined SOZ discrimination using both patterns in different frequency bands and periods of interest.
Results: Activation patterns were proved to be consistent across more than 80% of recurrent ictal epochs. In all patients, whole-seizure mean activations were significantly higher for SOZ than non-SOZ regions ($P < 0.05$) while activation onset times were significantly lower for SOZ than for non-SOZ regions ($P < 0.001$) in six patients. Alpha-beta bands (8–20 Hz) achieved the highest patient-average effect size on the whole-seizure period while gamma band (20–70 Hz) achieved the highest discrimination values between SOZ and non-SOZ sites near seizure onset (0–5 s).
Conclusions: Consistent spectral activation patterns in focal epilepsies discriminate the SOZ with high effect sizes upon appropriate selection of frequency bands and activation periods.
Significance: The present method may be used to improve epileptogenic identification as well as pinpoint additional regions that are functionally altered during ictal events.

1. Introduction

The accurate identification of the epileptogenic zone in patients with medically refractory epilepsy is central to plan an efficient surgical intervention. Yet, after decades of surgical treatment experience, the outcome is not completely successful in a significant proportion of patients (Spencer and Huh, 2008) for several causes including complex epileptogenic networks, surgery technical limi-

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tations, among others. Nowadays invasive recording techniques such as stereoencephalography (SEEG) (Munari and Bancaud, 1985; Talairach et al., 1974; Guenot et al., 2002; Engel et al., 2005) provide a continuous monitoring tool for pre-surgical diagnosis that becomes specially effective in patients with challenging focal epilepsies. However, those patients exhibiting complex activation patterns across different seizures still represent a diagnostic challenge because they involve time-consuming EEG evaluations that may lead to inconclusive interpretations. Hence, the use of quantitative tools that assess the consistency of ictal patterns across recurrent seizures might contribute to objectively identify the epileptogenic zone, thus improving pre-surgical diagnosis (Engel et al., 2005) and reducing potential failures. In addition, quantitative measures might provide additional insights into the mechanisms of focal ictogenesis (Goodfellow et al., 2016) when correlated with available structural and functional information.

Over the last decade, several studies have proposed biomarkers to evaluate the epileptogenicity of recorded intracranial structures. A great number of them have analyzed spectral features of SEEG signals (Bartolomei et al., 2008; David et al., 2011; Gnatkovsky et al., 2011; Gnatkovsky et al., 2014; Andrzejak et al., 2015), which mimic the patterns that are visually identified as epileptogenic during diagnostic EEG inspection (Gnatkovsky et al., 2014; Lagarde et al., 2016). In these works, epileptogenic biomarkers are typically built around two variables, the activation of signal's spectral properties (e.g., the relative amount of signal power in a frequency band (Bartolomei et al., 2008)) and the onset time of this activation, which measure respectively the amount of ictal activity and the degree of early participation of such structures during seizures. Epileptogenicity is then defined for each structure by combining both variables into an index that may be averaged across distinct seizures (Bartolomei et al., 2008; David et al., 2011; Andrzejak et al., 2015) to obtain a single biomarker per region. Critically, these mathematical transformations leading to a single value per region might prove inaccurate when averages are performed across seizures with heterogeneous activation patterns.

In the current study, we developed a flexible, robust and visual-friendly computer-aided method to assess the homogeneity of two ictal-driven channel spectral patterns (mean power change and power change onset time) across recurrent focal seizures. We evaluated the method in a group of seven epileptic patients with temporal lobe drug-resistant focal seizures. In all patients, we obtained seizure averages of both activation patterns for each recorded channel that were represented in two-dimensional plots for complementary clinical evaluation. As an example of application, we used each averaged pattern to characterize the seizure onset zone (SOZ) of seven patients with well identified seizure focus and tested the variability of the results obtained against the main method's parameters. The proposed procedure may be integrated into existing epileptogenic indices by choosing the frequency band of interest and appropriately plugging in each averaged pattern, thus contributing to identify in a robust form central regions in the generation and spread of focal seizures.

2. Methods

2.1. Ethics statement

All diagnostic and surgical procedures were approved by The Clinical Ethical Committee of our Hospital.

2.2. Patients and recordings selection

A total number of 46 focal seizures from seven patients with pharmacoresistant epilepsy were analyzed. A summary of all patients' characteristics is given in Table 1. Seizure onset and termination times of each seizure were independently marked by two epileptologists (RR and AP) using standard clinical assessment. For each seizure we analyzed SEEG recordings from the marked ictal epoch together with 60 s of pre-ictal and 60 s of post-ictal epochs.

We selected seven patients in which the seizure focus had been marked by epileptologists under the general principle that "the ictal onset was confined to a certain number of contacts and it was stable through ictal events". Among the selected patients, Patients 1–3 achieved seizure freedom after surgical resection (Engel I) with a follow-up period of at least two years. Patients 4 and 5 underwent radiofrequency thermocoagulation (RFTC, Bourdillon et al., 2017) and have showed favorable outcome over the last two years (see Table 1). Patient 4 is now seizure free, while Patient 5 has proven to be responsive to RFTC showing a seizure reduction larger than 50%. We also selected two patients (Patients 6 and 7) in which the outcome had not been successful because the brain resectomy had failed to completely remove the identified seizure focus. In particular, in Patient 6 the seizure focus could not be removed because it overlapped with eloquent areas.

All recordings were obtained using a standard clinical EEG system (XLTEK, subsidiary of Natus Medical) with a 500 Hz sampling rate. A uni- or bilateral implantation was performed accordingly, using 5–15 intracerebral electrodes (Dixi Medical, Besançon, France; diameter: 0.8 mm; 5–15 contacts (or channels), 2 mm long, 1.5 mm apart) that were stereotactically inserted using robotic guidance (ROSA, Medtech Surgical, Inc). The decision to implant, the selection of the electrode targets and the implantation duration were entirely made on clinical grounds.

2.3. Data pre-processing

EEG signals were processed in the referential recording configuration (i.e., each signal was referred to a common reference). The electrodes per patients included in the analysis are reported in Table 1. All recordings were band-passed filtered (FIR, filter band [1,165] Hz) to remove slow drifts and aliasing effects and notch-filtered to remove the effect of the alternate current (Notch FIR filter at 50 Hz and harmonic frequencies). Channels with artefacts were identified by visual inspection and removed prior to data analysis. For the precise estimation of activation onset times, artefacts simultaneously affecting the majority of SEEG channels during short instances were removed using the following systematic procedure. We performed a sliding-window analysis (200 samples width, 1 sample step) along seizure epochs and identified those time windows where the product of the mean correlation and the channel-average signal power was two standard deviations larger than the median.

2.4. Data analysis

2.4.1. Instantaneous activation

We used the Hilbert transform method (Le Van Quyen et al., 2001; Oweis and Abdulhay, 2011) to obtain a spectrogram of the signal recorded by each channel with a time resolution of 2 ms (Fig. 1A and B). The signal was split into non overlapping narrow frequency bands $[f, f+\Delta f]$, with $\Delta f = 0.1f$, starting at $f = 3$ Hz and up to $f = 160$ Hz. Summation of the spectrogram over a given frequency band was performed to collapse the information along one axis, thus obtaining the instantaneous power per channel (Fig. 1C). This step was primarily done over all analyzed frequencies and was later particularized to specific frequency bands. A baseline pre-ictal distribution of power was defined by accumulating the power values of all channels during the first 40 s of the pre-