Epileptogenicity Mapping
A Quantitative Approach to Identify the Seizure Onset

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KEYWORDS

• Epileptogenicity mapping • Seizure onset zone • Computerized analysis
• Intracranial electroencephalography

KEY POINTS

- Quantitative intracranial EEG provides tools to interpret recorded signals.
- Several features can be used separately or at the same to characterize the seizure onset zone and propagation networks.
- Epileptogenicity mapping using ictal high gamma oscillations is implemented in Brainstorm open-source software.

INTRODUCTION

To go beyond the gold-standard visual analysis of intracranial electroencephalogram (IEEG), for localizing the seizure networks involved in refractory focal epilepsies, it is useful to develop quantified biomarkers that can be used during presurgical evaluation. The delineation of the epileptogenic regions is indeed a crucial objective to maximize the chances of seizure freedom. Quantitative intracranial electroencephalogram (QIEEG) is the modern approach that derives quantitative features from IEEG signals to prospectively delineate epileptogenic circuits, which are sometimes difficult to fully assess by standard visual inspection. Typically, these methods attempt to quantify the local changes of various types of neural activities during seizure. The complete delineation of the seizure onset zone (SOZ), however, may remain elusive because of the complex organization of networks involved in seizure generation.[1] Over the past decades, the problem of localizing the SOZ from IEEG recordings in drug-resistant epilepsies has fostered the development of quantitative tools and biomarkers to better characterize and interpret ictal genesis and its propagation.

The simplest approach for investigating the epileptogenic networks is by mapping the level of activation of each IEEG contact, of which the authors provide a comprehensive review on the existing methods. Other techniques, however, include functional connectivity analysis of IEEG, either measuring linear (coherence, linear regression) or nonlinear (mutual information, nonlinear regression, and similarity index) properties, in either time, frequency, or time-frequency domain. In addition, methods on causality analysis identify the network leader, whereas methods based on graph theory analysis attempt to describe both the global and the local characteristics of the epileptogenic networks based on pair-wise interactions. For a complete review on this topic, see

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Ref.[2] Going through methods mentioned above is out of the scope of this article; hence, biomarkers and quantification methods are concentrated on analysis of IEEG changes at seizure onset and their level of activation (for a recent review, see also Ref.[3]).

Seizure onset is characterized by dynamic changes in brain rhythms. Several patterns of seizure onset have been observed, most commonly low-voltage fast activity (43%).[4] Numerous biomarkers were therefore proposed to characterize epileptogenicity based on selected spectral or time-frequency features. From the recent work of the group from Hospital del Mar in Barcelona, power spectral activation patterns in gamma band (20–70 Hz) were first studied, by which further enhanced data-driven method, based on the global spectral activation in different frequencies and the activation of entropy, was developed to find the temporal scale and frequency range of SOZ neural oscillations {VilaVidal:2019cr}.[5] In the earlier work from the Milan group, a wider range of frequencies (1–250 Hz) was reported to achieve discrimination between SOZ and non-SOZ.[6] Later, the same group considered adding more features to their methodology, for example, fast oscillations (80–120 Hz) with very slow transient polarizing shift and IEEG flattening.[7] The distribution of power values was more skewed in epileptic than in nonepileptic channels in all the 3 frequency bands, yet the method has been shown to be sensitive to artifacts.[8] With the development of machine learning methods, it is now possible to work more easily with multiple features. For example, recently, time-frequency patterns of preictal spikes, fast oscillatory activity, and concurrent suppression of lower frequencies were fed to a classifier and further mapped on MRI.[9] This approach uses the concept of fingerprint of the SOZ based on machine learning of multiple features {Grinenko:2018be}.[10] Another very recent study identified epileptic and nonepileptic channels based on skewness of power distribution for 5 to 80 Hz and high-frequency oscillations (HFOs) (80–250 Hz, ripple, and 250–500 Hz, fast ripple) during stage N3 sleep.

Further research considered coupling between different brain rhythms to localize the SOZ. Specifically, the phase of slow oscillations (1–25 Hz) and the amplitude of HFOs (80–150 Hz) have been compared and processed together using a modulation index and phase-locking value. The method has been reported to be more effective as a predictive feature of SOZ of ictal electrocorticographic recordings, than the amplitude of high gamma alone.[11–14] Numerous research groups have also implemented quantitative methods based on nonlinear features of IEEG signals, such as entropy, fractal dimension, and Hurst exponent, to name a few, in order to characterize a hyperexcitable tissue and epileptic region; for a full review on comparison of different methods, see Ref.[15,16] Although most IEEG network studies analyze ictal and preictal data, recent evidence suggests that interictal recordings are also informative for localizing epileptic networks.[17]

Among those potentially complex measurements, 1 very simple, well-studied, and reliable biomarker to localize epileptic regions has been shown to be low-voltage fast activity (30–120 Hz), possibly accompanied with a very slow transient polarizing shift at the seizure onset contacts.[18–20] Increasing evidence has been collected over the past decade underlying that HFOs greater than 80 Hz can be another potent biomarker for the epileptogenic zone,[21] after several studies reported successful surgical outcome after removal of regions with high HFO rates (for a review, see Ref.[22]). In a seminal work for QIEEG, the epileptogenicity index method introduced by the Marseilles group combines into a single and normative value of both spectral and temporal feature in a frequency range of 12 to 97 Hz, which can then be displayed on the patient's MRI.[18] A similar approach was suggested by the authors' group, in which they adopted a neuroimaging approach in order to generate statistical parametric maps of HFOs at seizure onset, commonly known as epileptogenicity map.[19] They successfully applied this methodology to a large number of epilepsy types.[23–25] Recently, from a short series of unselected cases, the authors showed that the epileptogenicity mapping procedure was significantly more efficient than visual analysis for the SOZ identification, and that it was predictive of surgery outcome at the group level.[26]

Importantly, the epileptogenicity mapping procedure, as published in Ref.[19] but with some improvements on the IEEG to MRI space mapping and frequency band selection procedure, has recently been implemented in the open-source Brainstorm software,[27] which is documented and freely available for download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm). Furthermore, the software provides a thorough step-by-step tutorial of how to compute maps of epileptogenicity from ictal recording (https://neuroimage.usc.edu/brainstorm/Tutorials/Epileptogenicity#Edit_the_contacts_positions). In later discussion, the authors describe the underlying methods and their practical use.

MATERIALS REQUIRED TO MAP SEIZURE NETWORKS FROM INTRACRANIAL ELECTROENCEPHALOGRAM

Preimplantation and Postimplantation MRI/ Computed Tomography of Patient

In order to produce the epileptogenicity maps, epileptogenicity values need to be interpolated on the anatomic MRI. A preimplantation MRI is used as the anatomic reference for a subject. Then, electrode position can be obtained by coregistering the preimplantation anatomic MRI with a postimplantation computed tomographic scan or structural MRI that displays the implanted electrodes.

Seizure Onset and Baseline Data Segments

Epileptogenicity maps can be produced for 1 or multiple seizures. Therefore, at least a minimum of 1 seizure per patient is required. Intersubject variation of seizure patterns can affect the epileptogenicity maps; therefore, in cases whereby multiple seizures exist for the same patient, in order to have a global picture of seizure originating regions, it is useful to cluster several seizures with the same semiology at a time. In this way, one can obtain multiple epileptogenicity maps: one for each seizure individually and another for a group of seizures with the same patterns. Each seizure needs to be inspected visually to determine an onset and a baseline period for the duration of about 20 seconds free from any artifact or epileptic activity.

Sufficient Spatial Sampling and Suitable Sampling Frequency

Mapping the seizure networks requires sufficient spatial sampling to produce meaningful images. In order to obtain precise localization of SOZ through QIEEG, surgical electrode implantation coverage and proximity to the SOZ are critical. The sampling rate of IEEG signal defines the maximum frequency band that can be analyzed. According to Nyquist theorem, if the frequency band of interest is less than 120 Hz, a sampling rate of 256 Hz could be sufficient. However, to study HFOs, at a higher frequency range of, for example, 400 Hz, the sampling rate required must be at least 1 kHz.

METHODS

Stereoelectroencephalography Power in Time-Frequency

In the clinical setting at Grenoble University Hospital, epileptogenicity is quantified as an increase of signal power in the 60- to 100-Hz band during seizure onset, as compared with interictal activity during a period preceding/following the seizure, depending which time window has less epileptic activity. Bursts of HFO lasting a few seconds at seizure onset have been proven to be a promising biomarker of the SOZ.[22] Hence, signal power in the time-frequency domain is computed for each electrode contact using the Morlet wavelet in successive time windows for both ictal and interictal periods. Because of the lack of homogeneity of IEEG amplitude, normalization needs to be performed to allow for a nonbiased comparison of different contacts. This normalization step is important for choosing visually an appropriate frequency band of interest of the SOZ identification. Finally, 2 log-transformed power distributions for each electrode contact are obtained, one for ictal and another for interictal period,[28] and the result of a statistical *t* test defines the epileptogenicity index.[19]

Spatial Interpolation of Features

Mapping seizure networks requires an accurate method to spatially interpolate the time-frequency features calculated above over the anatomy. Often IEEG analysis is performed on bipolar montage, providing sufficient spatial resolution of recorded signals, thus attenuating activities of distant sources that propagate through the brain volume. In addition, clinical interpretation of images is facilitated if IEEG images are produced using the same montage as the one used for visual inspection by neurologists. Provided that one has the electrode positions of IEEG and their corresponding feature vector of the QIEEG analysis, the simplest solution is to perform a spatial convolution of those points with a 3-dimensional (3D) Gaussian kernel. However, if the number of IEEG electrodes is insufficient, the results of the convolution might resemble an awkward collection of spheres distributed in the brain, for example, as in Ref.,[19] which leads to poor spatial rendering. To overcome the poor spatial rendering limitations, and extend the coverage of IEEG activity to white matter and the neocortical layer, specifically the hippocampus and the amygdala, the most studied structure for epilepsy surgery, the authors recently developed another interpolation technique that projects the IEEG onto meshes of desired above structures.[29] The interpolation algorithm works as follows: (i) For each electrode contact, the mesh vertices at a distance less than 1 cm are detected; (ii) To each vertex detected in the vicinity of at least 1 electrode, the assigned value is the average of the QIEEG values of the close electrodes, weighted by the

inverse of the distance between the vertex and the electrodes (more weight is given to the closest electrodes).

Statistical Parametric Mapping

Statistics can be obtained for each electrode contact separately or directly on images of log-power obtained after spatial interpolation as proposed in Ref.[19] In both cases, a correction for multiple comparisons needs to be applied to control the false positive rate. If statistics are obtained from images, statistical parametric mapping allows one to control family-wise error in the context of spatially correlated imaging data using the theory of Gaussian random fields.[30,31] The epileptogenicity values can be defined as the *t* values of the differences in smoothed log-power between ictal and interictal period. Statistical significance is directly obtained by the family-wise error-corrected associated *P* values. By applying a threshold on this *P* value, the regions showing significant rapid discharges at seizure onset can be identified. The same maps can be obtained at different values after seizure onset. It is then possible to look at how HFOs generated over a period of time, during the ictal period, and thereby to have a more complete picture of the seizure networks than only the SOZ.

CASE STUDY USING BRAINSTORM SOFTWARE

To illustrate the practical use of the Brainstorm software to produce epileptogenicity maps, the authors use data from a patient who was suffering from lesional partial epilepsy (mesial left occipital dysplatic lesion) with bilateral interictal abnormalities and contralateral ictal discharges (above right temporal region) on scalp electroencephalogram (EEG). The same data were used previously {Anonymous:2019uk},[32] in which more clinical information can be found. Stereoelectroencephalographic (SEEG) recordings (90 bipolar derivations in occipital, parietal, and temporal cortices and in hippocampus) showed lesional ictal onset in calcarine cortex with rapid spread to the fusiform gyri followed by bilateral discharges with right temporal lobe predominance (**Figs. 1** and **2**). This patient is now seizure-free with 3-year follow-up after resection limited to the occipital dysplastic region.

Data

The patient was fully informed of the clinical procedure and gave his consent before being implanted. Sixteen semi-rigid intracerebral electrodes were implanted. Each electrode was 0.8 mm in diameter and included from 5 to 15

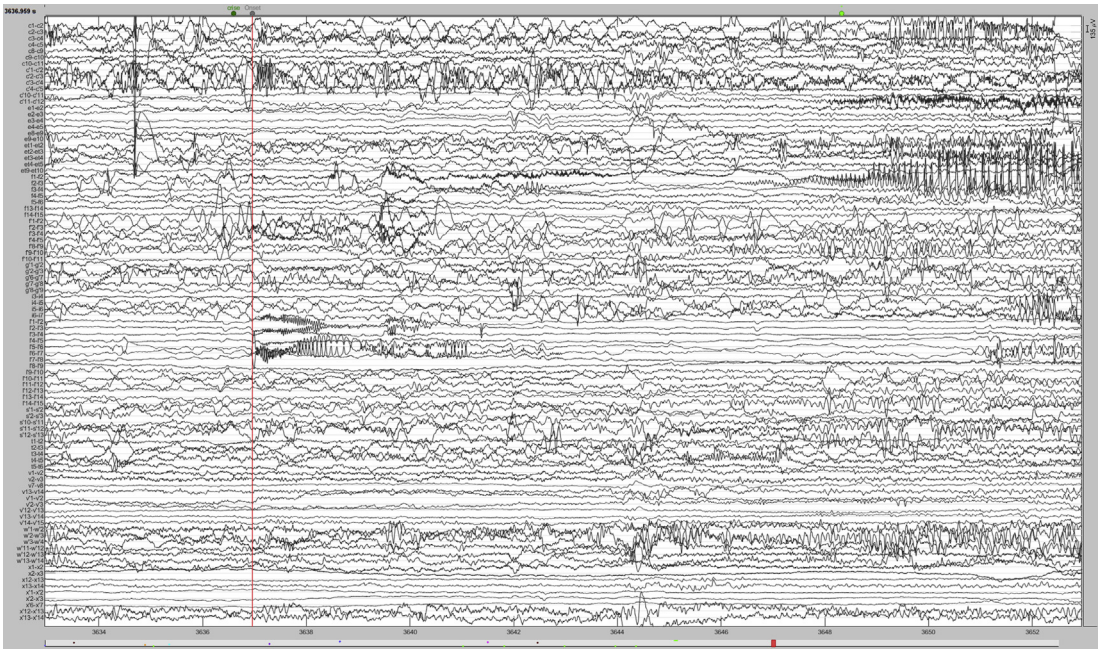

Fig. 1. SEEG traces displaying the beginning of a seizure. Fast oscillations can be seen at the seizure onset (*red line*) on electrodes r'6 to r'8.

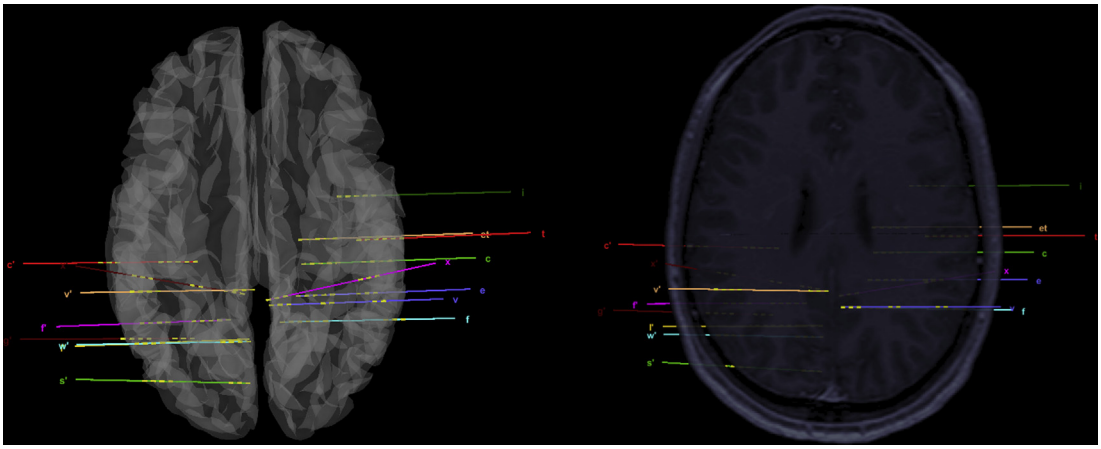

Fig. 2. SEEG depth electrode implantation rendered over the surface and preimplantation volume targeting the occipital lesion (not visible) and the bilateral temporal pathway displayed on the mesh of the cortex (*left*) and T1-weighted MRI (*right*).

leads 2 mm in length, 1.5 mm apart (Dixi Microtechniques, Besançon, France), depending on the target region (see Fig. 2). A preoperative stereotaxic MRI and a stereotaxic teleradiography matched with *Talairach and Tournoux*[33] *Stereotaxic Atlas* were used to assess anatomic targets. Implantation of the electrodes was performed in the same stereotaxic conditions, with the help of a computer-driven robot (Neuromate, Renishaw, Gloucestershire, UK). The location of the electrode contacts was subsequently reported on a stereotaxic scheme for each patient and defined by their coordinates in relation to the anterior commissure/posterior commissure plane.

SEEG recordings were performed using an audio-video EEG monitoring system (Micromed, Treviso, Italy). Sampling rate was 512 Hz, with an acquisition band-pass filter between 0.1 and 200 Hz, respectively. Data were acquired using a referential montage with reference electrode chosen in the white matter. For data analysis, the authors used a bipolar montage between adjacent leads of the same electrode to improve sensitivity to local oscillations. Coordinates of virtual bipolar electrodes that are used to construct images were chosen to be at equal distance of 2 successive contacts. The preimplantation MRI was used as the anatomic reference to coregister postimplantation T1 MRI volume where the location of SEEG implantation can be seen.

Epileptogenicity Map at Seizure Onset and Later

Two seizures were recorded during SEEG exploration. In later discussion, the authors present the analysis of only one of them (see Ref.[19] for the group analysis). Seizure was inspected visually to determine a baseline period and the seizure onset, that is, the exact timing of the first relevant electrical changes was marked as onset, as shown in Fig. 1. Seizure onset was defined from SEEG recordings using different patterns: (i) low-voltage fast activity over 20 Hz; (ii) recruiting fast discharge (around 10 Hz or more) of spikes or polyspikes; and (iii) rhythmic activity (around 10 Hz) of low amplitude. The origin of time for each seizure was determined from visual analyses just before suspected seizure onset. Baseline recording was chosen as a period of 20 seconds without strong artifact or epileptic activity during the 5 minutes preceding each seizure. The seizure-displayed HFOs originated from the dysplastic lesion before propagating to bilateral temporal regions (see Fig. 1). Fig. 2 displays the 3D implantation of the SEEG electrodes. This step can be performed with Brainstorm software or with other software solutions, for example, Intranat Electrodes from the authors' group.[34]

Epileptogenicity mapping successfully suggests a focal HFO onset on the dysplastic lesion (Fig. 3) with late diffusion to the rest of the temporal lobe through the ventral visual pathway, and very little involvement of parietal regions (Fig. 4). In Brainstorm, rendering can be done in 3D (see Fig. 3) or on the cortical surface (see Fig. 4). The epileptogenicity maps at the different perionset times were computed using a time window of 2-seconds' duration with a 2-second time step. Such information on the precise dynamics of HFO spatial patterns allowed the successful resection of the dysplastic lesion in left occipital

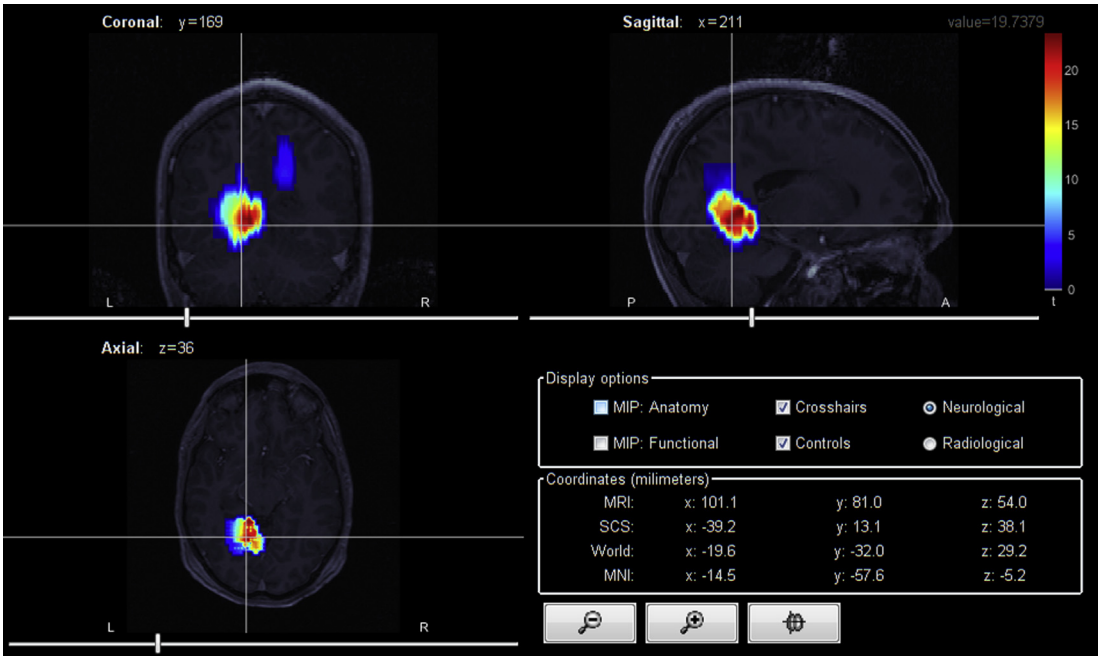

Fig. 3. Epileptogenicity 3D mapping showing the significant HFOs (60–200 Hz, *P*<.001, family-wise error corrected) at seizure onset. They were colocalized with the occipital dysplastic lesion.

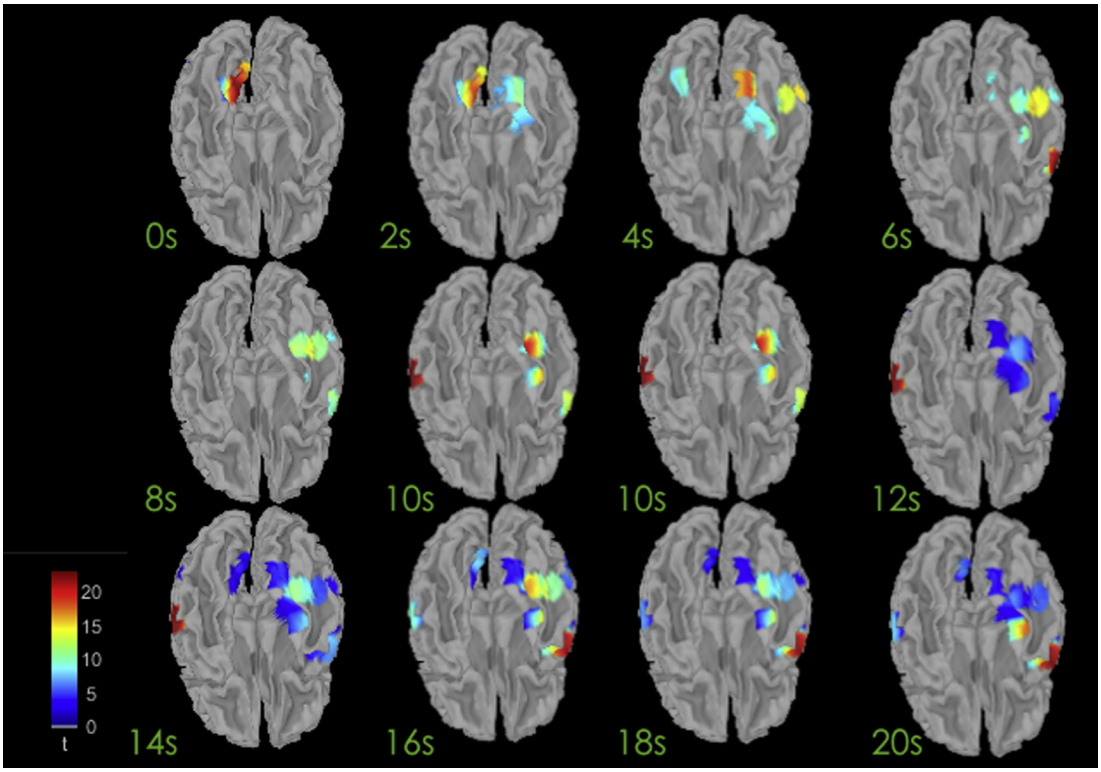

Fig. 4. Epileptogenicity surface mapping showing propagation of HFO activity during 20 seconds after seizure onset. Epileptogenicity surface mapping showing the spatial distribution of significant HFOs (60–200 Hz, *P*<.001, family-wise error corrected) at seizure onset and during the following 20 seconds. Note the early involvement of the left occipital lesion followed by the ventral occipital-temporal pathway up to the temporal pole.

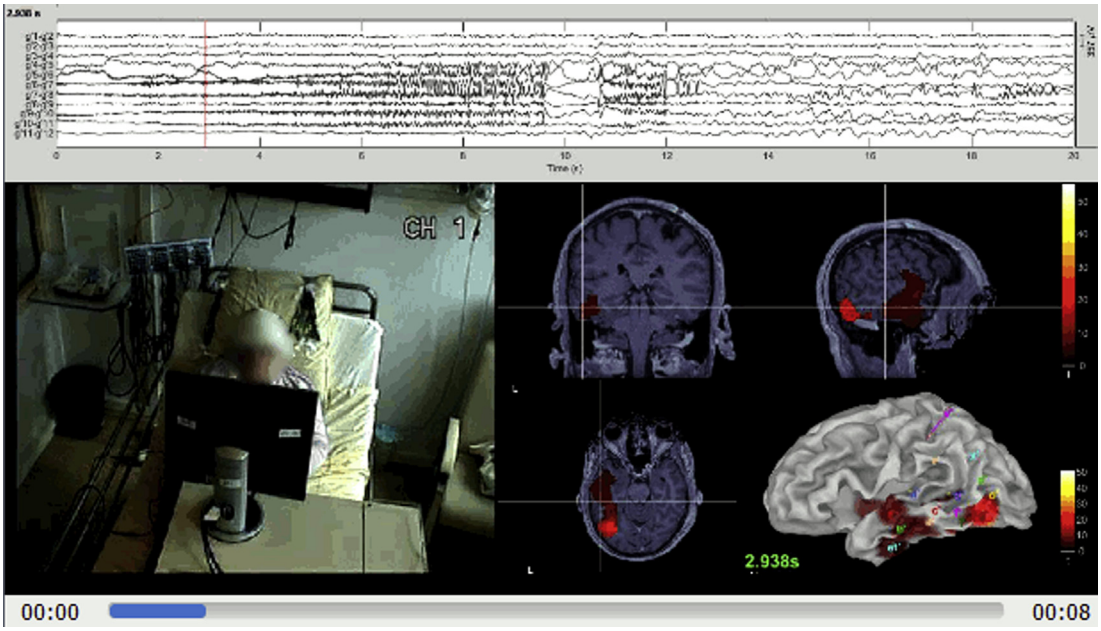

Fig. 5. Brainstorm interface to simultaneously review IEEG recordings, epileptogenicity maps, and video.

region, without considering surgery on temporal lobe regions.

EPILEPTOGENICITY MAPPING AND SEMIOLOGY CORRELATION

Epileptogenicity mapping quantifies changes in high gamma activities, which are also known to be correlated with behavior and cognition.[35] Therefore, it appears particularly relevant to investigate how the changes of ictal HFOs spatial patterns correlate with the semiology during seizures. To do so, the authors have implemented in the Brainstorm software the possibility to review IEEG recordings, epileptogenicity maps, and video in a synchronized fashion (**Fig. 5**). This type of integrated approach opens avenues for novel research studies that remain to be done. For more information on this topic, please refer to brainstorm tutorial (https://neuroimage.usc.edu/brainstorm/Tutorials/Epileptogenicity#Video-EEG).

SUMMARY

Nowadays, there are multiple QIEEG approaches to map the SOZ. It is very likely that new machine learning methods will make them more efficient in the near future. However, very few of them are now implemented in a user-friendly way. In this report, the authors wanted to introduce the recent effort they made to distribute the epileptogenicity mapping method in an open-source fashion, documented with full tutorials. In brief, epileptogenicity maps can be obtained with minimal interference (manual selection of seizure onset and baseline period), automatically and quickly, and using graphical user interfaces with Brainstorm software. Here, the authors presented results obtained in a lesional case using the high gamma range (100–200 Hz). From their experience, the choice of the precise limit of the gamma range is not critical in a certain range, that is, 40 Hz to 250 Hz, because the spatial pattern of epileptogenicity maps does not vary significantly with frequency greater than 40 Hz. Clearly, more focal maps are obtained for higher frequencies, but the structure of seizure networks is generally stable. Brainstorm implementation allows one to assess easily the effect of the frequency band on the epileptogenicity maps.

More generally, QIEEG methods from many laboratories have now reached a certain level of maturity, and the authors greatly encourage well-trained neurologists and neurosurgeons to use them and to assess their strengths and limitations for making progress on the presurgical assessment of epilepsy surgery.

DISCLOSURE

The authors have nothing to disclose.

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