

Value of seizure semiology and ictal source analysis in lateralizing and localizing the epileptic zone

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Background

Sophisticated analysis of seizure semiology and electroencephalography (EEG) has a significant role in lateralizing and localizing the epileptogenic zone. Hence, understanding the pathophysiology of epileptogenic dysrhythmia requires thorough knowledge of how to put the very different pieces of the puzzle together.

Objective

The aim of the study was to investigate the concordance between seizure semiology, electrophysiological generator, anatomical lesions, and neuropsychological evaluation in patients with partial epilepsy, and to identify the importance of ictal EEG recording and the diagnostic yield of other electrophysiological techniques.

Patients and methods

Thirty patients with a diagnosis of intractable partial epilepsy and lesional MRI were prospectively included. All of them were clinically evaluated and identified according to semiological seizure classification. Long-term video digital EEG with ictal recording was done, along with a source analysis (SA) study.

Results

Clinical evaluation by seizure semiology lateralized 73% of the cases and localized 80%. Ictal EEG lateralized 80% of cases and localized 66.9%. SA revealed a much superior power to lateralize and localize (96.7%) the epileptogenic zone, but what is more important is the added value of SA, as it lateralized and localized 96–100% of the cases that failed on semiology. SA has the highest expected value for additional lateralizing and localizing information (± 7.73 and ± 7.30 , respectively).

Conclusion

Seizure semiology and ictal EEG recording with SA are the most accurate ways to lateralize and localize the epileptogenic zone in intractable partial epileptic cases, giving the patient a respectable chance to avoid other invasive diagnostic techniques.

Keywords:

epileptic zone, ictal, semiology, source analysis

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Introduction

Epilepsy consists of more than 40 clinical syndromes affecting 50 million people worldwide. Approximately 25–30% of patients receiving medication have inadequate seizure control. Drawing on advances from the epilepsy field and other rapidly changing fields of biomedicine, it was proposed to shift the focus of research to curing epilepsy, which involves prevention of epilepsy in people at risk, and effective and safe treatment, meaning absence of seizures and side effects in people with epilepsy [1].

In many cases, complicated generator configurations underlie electroencephalography (EEG) recordings, involving multiple focal sources. Therefore, it is necessary to apply different methods to the same data set to obtain converging evidence and conclusions [2]. In the process of localization of

source activity, because the electrophysiology of the brain is very complicated, EEG is roughly divided into event-related potentials and spontaneous activity. Both can refer to generalized brain localization; yet, some event-related potentials can refer to specific localization [3]. Herein lies the importance of studying seizure semiology and its relation with the generator zone [4].

Hence, understanding the pathophysiology of epileptogenic dysrhythmia requires knowledge of how to put the very different pieces of the puzzle together.

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In other words, we should identify the value of each piece and its relation to the others.

Sophisticated analytical methods for EEG play a key role in the better understanding of brain functions as measured by high-density EEG [5]. Advances in technology to localize focal epileptogenic substrates especially that of high-resolution structural imaging have substantially improved the success of surgical treatment [6].

Aim

The aim of this investigation was to study the relationship between seizure semiology, electrophysiological generator, and anatomical lesions in patients with partial epilepsy. We also aimed to identify the importance of ictal EEG recording and verify the diagnostic yield of other electrophysiological techniques.

Patients and methods

The study included 30 patients, prospectively recruited, suffering from medically intractable partial epilepsy, with or without secondary generalization, who were older than 15 years, and with lesional brain MRI. Nineteen patients were male and 11 were female. Patients' ages ranged between 15 and 71 years, with a mean of 32.33 years. The duration of illness was between 3 and 27 years, with a mean duration of 11.77 years.

All patients were subjected to a series of procedures:

- (a) Clinical evaluation by history and seizure semiology;
- (b) Semiological identification according to Lüder's classification [4,7];
- (c) Seizure type identification according to the syndromic classification [8];
- (d) Long-term video digital EEG with ictal recording of at least three seizures using a Galileo Mizar 40-channel machine (EBNeuro SpA, Florence, Italy) (EEG data were acquired with 25 electrodes using a 10–20 system, including additional anterior–inferior electrodes); labored hyperventilation and extensive photic stimulation, together with sleep deprivation prior the recording day, were used for seizure provocation;
- (e) Dipole Localization Method and Multiple Signal Classification Analysis (MUSIC) using ASA version 2 (ANT Software BV, Enschede, the Netherlands). Both ictal and interictal EEG recording were analyzed in a blinded manner, these

readings were traced during the video digital EEG recording, using manual spike identification, and plotting of the results on the patient's brain MRI (DICOM format);

- (f) Blinded cognitive testing using the Luria–Nebraska Neuropsychological Localization Scale (LNLS) [9].

The data derived from all procedures and methods adopted in the study were presented in the form of descriptive statistics. Statistical significance testing for the power of the electrophysiological and neuropsychological methods to lateralize and localize the epileptogenic zone was done using the χ^2 distribution with Yates' correction (when at least 20% of expected frequencies are <5). The reliability of the added value of each significant method was tested using the confidence intervals test [10].

Results

Semiological, electrophysiological, radiological, and neuropsychological evaluations were analyzed in two axes: first, the lateralizing value (the power to lateralize the cerebral hemisphere of origin), and second, the localizing value (the power to localize the epileptogenic zone within the cerebral hemisphere).

We assumed theoretically that the lesion in the MRI is the epileptogenic zone or at least the main generator in the studied cases. The localization ability of electrophysiological and neuropsychological techniques was identified by whether the findings were focal (only one focus), regional (more than one unilateral focus, or same area bilaterally), hemispheric (all lobes of one cerebral hemisphere), generalized (including bilateral origins), or uneventful. The concordance between every method, including the clinical semiology, and MRI was ascertained and rated by whether the findings were concordant, concordant plus (with additional ipsilateral localization data), or discordant.

All patients underwent MRI with FLAIR coronal cuts. Only one patient underwent a diffusion tensor imaging (DTI). Mesial temporal sclerosis was found in 11 (36.7%) cases, space-occupying lesions in seven (23.3%) cases, encephalomalacia and gliosis in nine (30%) cases, cortical dysplasia in one case, vascular infarction in one case, and nonspecific hyperintensity in one case. The only case to have undergone a DTI showed right hippocampal dysfunction confirming the routine MRI finding.

Clinical evaluation by seizure semiology was able to lateralize 24 (80%) cases and localize 28 (93.3%).

The concordance between semiology and MRI was achieved in 22 (73.3%) cases for lateralization, and in 11 (36.7%) cases for localization. Concordant plus was observed in 13 (43.3%) cases (Fig. 1).

Of the 28 cases localized by clinical semiology of seizures, 13 (43.3%) cases were frontotemporal in origin, nine (30%) cases were temporal, five (16.7%) cases were frontal, and only one case was frontoparietal.

Seventeen (56.7%) cases reported either single or multiple types of auras. Only four (13.3%) cases experienced automatism (automotor seizures). Secondary generalization was recorded in 23 cases: either losing consciousness (dialectic seizures) in 11 cases or generalized tonic-clonic seizures in 17 cases, with five cases experiencing both types of generalization.

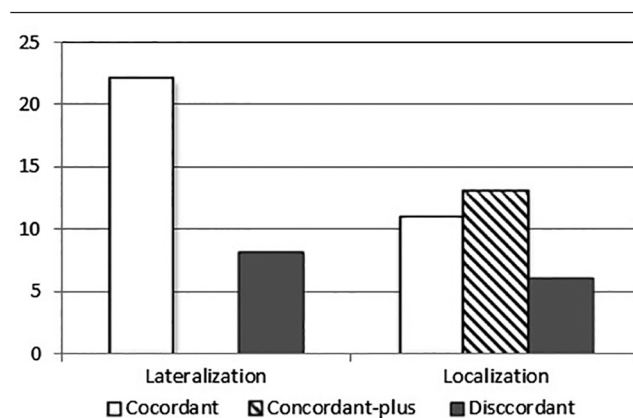
Interictal EEG lateralized 14 (46.7%) cases, whereas 13 (43.3%) cases showed subcortical dysrhythmia and three (10%) cases were uneventful. Of the 30 cases included in the study, seven (23.3%) were focal, four (13.3%) were regional, five (16.7%) were hemispheric, 11 (36.7%) were generalized, and three (10%) were uneventful. The concordance between interictal EEG and MRI was achieved in 14 (46.7%) cases for lateralization, whereas for localization it was concordant only in eight (26.7%) cases and concordant plus in two (6.7%) cases.

Ictal EEG lateralized 25 (83.3%) cases, and it failed to lateralize only five (16.7%) cases; four of them showed bilateral dysrhythmia and one case showed subcortical dysrhythmia. Of the 30 cases, ictal EEG showed six (20%) cases with focal origin, 16 (53.4%) with regional origin, seven (23.3%) hemispheric, and only one (3.3%) generalized. The concordance between ictal EEG and MRI was achieved in 24 (80%) cases for lateralization, whereas for localization it was concordant in 11 (36.7%) cases and concordant plus in nine (30%) cases (Fig. 2).

Source analysis (SA) using the dipole and MUSIC techniques lateralized 29 (96.7%) cases, and failed to lateralize only one case, although this case was lateralized by ictal EEG. Of the 30 cases, SA showed 17 (56.7%) cases with focal origin, 12 (40%) regional, and only one (3.3%) generalized. The concordance between SA and MRI was achieved in 29 (96.7%) cases for lateralization, with only one discordant case that was discordant by all other used methods, whereas for localization it was concordant in 21 (70%) cases and concordant plus in eight (26.7%) cases (Fig. 3).

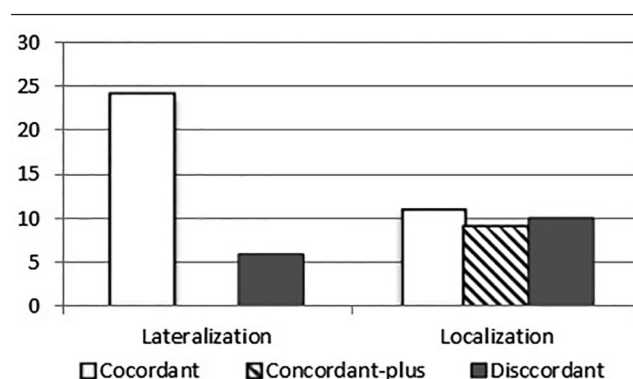
Neuropsychological evaluation with the LNLS lateralized only seven (23.3%) cases; these were the same cases that LNLS could localize as regional. The

Figure 1



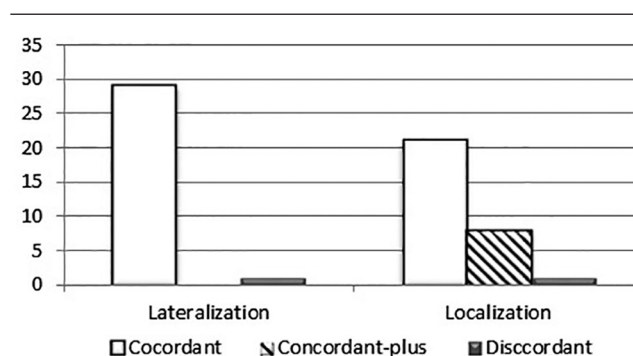
Semiology and MRI concordance.

Figure 2



Ictal electroencephalography and MRI concordance.

Figure 3



Source analysis and MRI concordance.

concordance between LNLS and MRI was achieved in only five (16.7%) cases for lateralization, and in only two (6.7%) cases for localization. Concordant plus was reached in five (16.7%) cases, whereas the remaining 23 (76.6%) cases were discordant.

It is noted that SA achieved the best concordance with MRI, followed by the ictal EEG; the interictal

EEG with the neuropsychological evaluation was the least concordant technique. Because of that, neuropsychological evaluation was excluded from some of the further statistical tests.

Concordance was then tested head to head, and the power of different techniques together to lateralize and localize was analyzed statistically. Interictal EEG was found to be the least powerful technique to lateralize when tested against the other three techniques. It was evident that the SA ($P = 0.00001$) was the most significant technique, followed by ictal EEG ($P = 0.007$) and then semiology ($P = 0.035$), compared with interictal EEG. SA was also significantly more powerful than semiology ($P = 0.03$). However, the difference between SA and ictal EEG was insignificant ($P = 0.1$).

The correlation of the used techniques in localizing the epileptogenic zone was found to be highly significant. LNLS was the least powerful technique to localize when tested against the other four techniques. It was evident that SA was the most significant technique, followed by semiology and ictal EEG. SA was significantly more powerful than ictal EEG, but it was insignificantly different than semiology (Table 1).

Finally, the added value of each method, from the practical clinical point of view, over semiology was estimated using the confidence interval test (Table 2).

This revealed that SA has the highest expected value for additional lateralizing and localizing information. The added value for lateralization was reasonable for the three used techniques, especially for the SA. However, the added value for localization was only reasonable for SA.

Discussion

Epileptogenesis is thought of as a cascade of dynamic biological events altering the balance between excitation and inhibition in neural networks. The term applies to any of the progressive biochemical, anatomic, and physiologic changes leading up to recurrent seizures [11,12].

In 1993, Lüders *et al.* [13] called for a seizure classification based exclusively on ictal clinical semiology. They also believed that all additional clinical information such as clinical history, neurological examination, seizure evolution, EEG recording, anatomic neuroimaging, and functional neuroimaging should be analyzed separately, and then integrated to precisely define the epileptic syndrome [13]. They introduced in 1998 an overview of this seizure classification that is based exclusively on ictal seizure semiology, either as reported by a witness or as analyzed directly during video recording, and named as the semiological seizure classification [14].

The limitations of witnesses in accurately and fully describing seizures may be a reason for the difficult identification of seizure type on the basis of the history even by expert clinicians. Hence, video recordings of seizures confirm the seizure description obtained from the patient history [15]. So [16] confirmed, most features are useful for lateralizing seizure onset to a hemisphere, whereas few features help in localizing seizure onset to a more accurate location.

Blinded analysis of video-recorded seizure semiology showed that 82% of temporal lobe seizures and 87% of frontal lobe seizures could be lateralized [17], with correct results in 90% of the temporal lobe seizures and in 95% of the frontal lobe seizures. Another study showed that the concordance between seizure semiology and ictal scalp EEG was more than 95% in temporal lobe epileptic patients [18]. The difference between interictal and ictal EEG recording power to both lateralize and localize was statistically significant, placing the ictal EEG recording for intractable patients as the first priority and of course of superior value to the routine interictal EEG. However, when comparing both EEG modalities with semiological abilities to lateralize and localize, there was no significant difference between interictal and ictal EEG in adding information as they were both able to lateralize and localize 86–90% of the cases failed by semiology.

Applying SA, using both the dipole and MUSIC techniques on all cases, revealed a much superior power

Table 1 The correlation between techniques in localization

Techniques	Interictal EEG	Semiology	Ictal EEG	Source analysis
Luria–Nebraska localization scale	$\chi^2 = 0.7$ $P = 0.4$	$\chi^2 = 19.29$ $P = 0.00001^*$	$\chi^2 = 11.38$ $P = 0.0007^*$	$\chi^2 = 33.61$ $P = 0.0000^*$
Interictal EEG	–	$\chi^2 = 13.30$ $P = 0.0003^*$	$\chi^2 = 6.66$ $P = 0.01^*$	$\chi^2 = 26.44$ $P = 0.00000^*$
Semiology	–	–	$\chi^2 = 1.36$ $P = 0.2$	Yates $\chi^2 = 2.59$ Yates $P = 0.1$
Ictal EEG	–	–	–	Yates $\chi^2 = 9.02$ Yates $P = 0.003^*$

EEG, electroencephalography; *Significant.

Table 2 The expected added value for each method over semiology

Techniques	Lower limit	Upper limit	Confidence interval
Lateralization			
Interictal EEG	3.35	30.00	±6.81
Ictal EEG	3.35	30.00	±6.81
Source analysis	8.24	38.55	±7.73
Localization			
Interictal EEG ^a	-2.25	15.65	–
Ictal EEG ^a	-0.74	20.74	–
Source analysis	5.69	34.31	±7.30

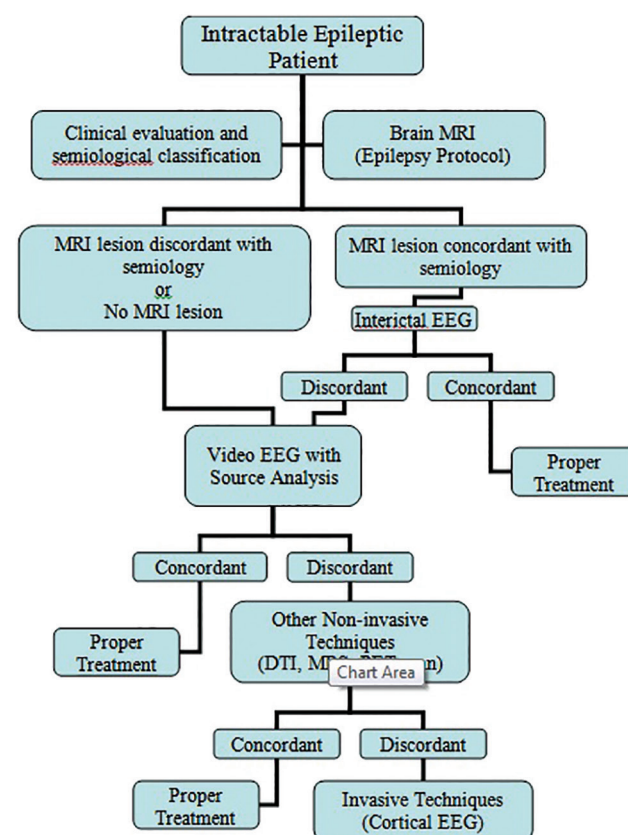
Values are represented as %; EEG, electroencephalography;

^aConsidered insignificant as zero% is included.

to lateralize and localize (96.7%) the epileptogenic zone. However, what is more important is the added value of SA, as it lateralized and localized 96–100% of the cases failed by semiology. These results were higher than the results shown by Boon *et al.* [19] and Herrendorf *et al.* [20], who attributed their poor results to the deep epileptogenic source in the cases enrolled in their study. Our results agreed with those of Gaber *et al.* [21], who revealed the significance of the SA techniques in lateralization and localization up to 96%. Our results are also commensurate with the findings of Verhellen and Boon [22], who critically reviewed the results of relevant EEG source localization studies in patients with refractory temporal lobe epilepsy that were published in the earlier decade, and assessed the reliability and limitations of this technique. They concluded that dipole modeling of interictal and ictal EEG signals is able to represent cerebral sources in an accurate and noninvasive way [22]. In addition, these promising results go with other more recent studies that showed similar results regarding the value of EEG SA studies [23–25].

Conclusion

The benefit of our study from a clinical point of view is that a real in-clinic situation is presented and a suggestion is put forth on how an epileptologist should act. When a patient with intractable epilepsy presents at the clinic, after clinical and semiological evaluation, and after undergoing an MRI (routine epilepsy protocol), the patient is placed in either of two groups. The first group includes patients with a lesion in their brain MRI that is concordant with the clinical and semiological evaluation. The second group includes patients with a lesion that is discordant with the clinical and semiological evaluation, or even with no brain MRI lesion. The next proposed step is to follow our proposed algorithm shown in Fig. 4. Further studies are recommended with more electrodes to cover the inferior areas of the brain, in addition to studies to

Figure 4

A suggested flow chart for managing intractable epileptic patients. DTI, diffusion tensor imaging; EEG, electroencephalography.

evaluate the added value of these different techniques, especially in relation to either other noninvasive techniques including interictal and ictal SPECT, PET scan, and DTI, or invasive ones such as cortical EEG recording, as well as perform comparative postsurgical outcome evaluation.

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Conflicts of interest

There are no conflicts of interest.

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