Original Article

# Electrical source localization by LORETA in patients with epilepsy: Confirmation by postoperative MRI

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## Abstract

**Background:** Few studies have been conducted that have compared electrical source localization (ESL) results obtained by analyzing ictal patterns in scalp electroencephalogram (EEG) with the brain areas that are found to be responsible for seizures using other brain imaging techniques. Additionally, adequate studies have not been performed to confirm the accuracy of ESL methods. **Materials and Methods:** In this study, ESL was conducted using LORETA (Low Resolution Brain Electromagnetic Tomography) in 9 patients with lesions apparent on magnetic resonance imaging (MRI) and in 6 patients who did not exhibit lesions on their MRIs. EEGs of patients who underwent surgery for epilepsy and had follow-ups for at least 1 year after operations were analyzed for ictal spike, rhythmic, paroxysmal fast, and obscured EEG activities. Epileptogenic zones identified in postoperative MRIs were then compared with localizations obtained by LORETA model we employed. **Results:** We found that brain areas determined via ESL were in concordance with resected brain areas for 13 of the 15 patients evaluated, and those 13 patients were post-operatively determined as being seizure-free. **Conclusion:** ESL, which is a noninvasive technique, may contribute to the correct delineation of epileptogenic zones in patients who will eventually undergo surgery to treat epilepsy, (regardless of neuroimaging status). Moreover, ESL may aid in deciding on the number and localization of intracranial electrodes to be used in patients who are candidates for invasive recording.

## Key Words

Epilepsy, epileptogenic zone, LORETA, postoperative MRI, source localization

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## Introduction

Localization of the sources of electroencephalographic (EEG) activity in the brain is important in both clinical[1] and basic[2] research. Quantitative localization of EEG brain sources began in the 1950s with investigations to determine the nature of scalp surface potential distributions that reflect sources in the brain.[3,4]

Electrical source localization (ESL), also known as electrical source imaging, is a model-based imaging technique that integrates temporal and spatial components of EEG to identify the source of electrical potentials recorded on the scalp.[5] ESL techniques have been widely studied and validated for the study of inter-ictal[6-12] and ictal ESL.[13-17] However, only a few studies have compared the analyses of different types of ictal activity.[18,19] Although a template head model is generally preferred in ESL studies, individual head models obtained from the patients' own magnetic resonance images (MRIs) are also used. However, constructing an individual head model for a patient to estimate and confirm the epileptogenic zone is an onerous process.[20-30]

The clinical benefits of information derived from ESL were first shown in patients with lesioned epilepsy.[31-33] Some recent

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studies have shown furthermore that the brain area causing the seizures in temporal lobe epilepsy (TLE) and extra-temporal lobe epilepsy (ETLE) could be determined using ESL, even when the disorder was not detected in MR images.[29,34] However, very few studies have utilized ESL in recent years to determine the location of the epileptogenic zone in ETLE, especially in cases where MR images appear normal. This can be attributed to the fact that such attempts require well-planned prospective studies, which should be based on long-term surgical outcome and sufficient number of patients in order to be meaningful statistically.

In the present study, ESL was performed using a method called "low-resolution electrical tomography"[35-38] for the estimation of epileptic zone from different forms of scalp EEG ictal activity. Main goals of the study were:

1. To assess the contribution of the ESL method for determination of the epileptic zone in patients with and without lesions on MRI;
2. To determine the impact of using the patient's own MRI scan on the accuracy of ESL; and
3. To investigate the effect of scalp EEG ictal activity on the performance of ESL.

## Materials and Methods

### Subjects

The data examined in our study were from 15 patients with drug-resistant focal epilepsy who were candidates for surgery. Informed written consent was obtained from each patient, and the study was approved by the ethics committee of the Istanbul University, Cerrahpaşa Medical Faculty.

For this study, we used the following inclusion criteria to select patients from our database who:

1. Had drug-resistant focal epilepsy.
2. Underwent pre-surgical evaluation and long term video-EEG recording .
3. Had post-surgical MRI performed according to an epilepsy protocol.
4. Had surgery and follow-up for at least 14 months.

The characteristics of all the patients are tabulated in Table 1. The age range of patients was 5-47 years. (mean: 23.07; median: 23). Five of the patients were female. In pre-surgical evaluations, the epileptogenic zone of 11 participants was described as temporal, and that of four patients was identified as extra-temporal.

The pre-surgical evaluations included neurological examinations, long-term video-EEG monitoring, MRI performed according to an epilepsy protocol, fluorodeoxyglucose positron emission tomography (PET), and neuropsychological evaluation. Eight patients underwent a second evaluation phase involving intracranial recording.

### EEG scalp/surface recording

Long-term video-EEG recording with 64 scalp electrodes (SynAmps; Compumedics Neuroscan, Charlotte, NC, USA, or SD LTM64 Headbox; Micromed, Italy) was performed on all patients using a standard clinical EEG setup. Electrodes were placed according to the 10-20 montage international system. Impedances were below 5 kΩ. The signal was sampled at 256 Hz and digitized, and the stored data was off-line filtered using 0.5-100 Hz band-pass digital filters.

### Scalp-EEG ictal detection, selection, and analysis

Ictal activity was categorized as follows according to the classification of:[18]

1. Ictal spike activity: A wave in the form of spike recorded during epileptic seizures. Three or more discharges in sequence.
2. Rhythmic activity: EEG waves (alpha, theta or delta) that is up to 13 Hz frequencies.
3. Paroxysmal fast activity: The rhythmic activity that is bigger than 13 Hz frequency.
4. Obscured activity: Pattern evolves from artifact such that precise time, pattern, and distribution of onset was imperceptible.

Advanced Signal Analysis (ASA) software (ANT Software, Enschede, The Netherlands) was used for selection, detection, and analysis of scalp-EEG ictal patterns. For ESL with LORETA analysis, seizures were divided into several events subsequent in time. Time analysis windows of each event ran from the start to the end of the change in amplitude.

### Localization of electrode position

The fiducial system was used for localization of EEG electrodes for all patients, which were defined by marker points (the nasion and the right and left tragi) and registered by automatic localization and labeling of EEG sensors in the MRI volume.[39]

### MRI and individual head model

MRI scans for all patients were acquired as a part of the post-surgical evaluation with 1.5 T scanners according to an epilepsy protocol. These post-surgical MRI scans were used for obtaining an individual head model for each patient. T1-weighted sequences with pixel size of 0.98 $mm^2$, and slice thickness of 1.25 mm were used to obtain three-dimensional (3D) MRIs. In order to construct individual head models, geometrical boundaries of brain were defined using anatomical marker points (nasion, and right and left tragi), which are identical to those used in 3D MRI. The same spatial reference was identified for neurophysiological and structural data. The Boundary Element Method (BEM), being one of the most preferred methods, was also used for individual head models. Based on this method, segments of the three compartment surfaces (brain, skull, and scalp) were described by 4000 nodes per head model. According to this data, a realistic EEG transfer matrix was calculated. ASA software was used for the processes mentioned above. Specific conductivity values attributed to the brain, skull, and scalp of each patient were 0.33, 0.0042, and 0.33 Siemens/meter, respectively.

### LORETA

The low resolution electromagnetic tomography method (LORETA) was used to determine brain electrical sources. LORETA is a Laplacian weighted minimum norm algorithm, which depends on the existing neuro-anatomical and physiological knowledge and a mathematical constraint.[40] The method is based on the reconstruction of the electric activity

**Table 1: Characteristics of the patients in terms of gender, age, ictal EEG localization, MRI and PET reports, operation region, pathology result, follow-up time after surgery, and seizure outcome, respectively**

| Patient | Gender | Age | Ictal EEG localization | MRI | PET | Operation side | Pathology | Postoperative follow-up time | Postoperative seizure condition |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 23 | Left anterior cingulate or orbitofrontal | Normal | Normal | Left frontal | FCD Type I | 23 months | Absent |
| 2 | M | 26 | Left frontotemporal | Normal | Left temporal lobe hypometabolism | Left temporal | FCD Type II | 26 months | Absent |
| 3 | M | 19 | Left parieto-occipital | Normal | Left inferior temporal lobe hypometabolism | Left parietal | FCD Type I | 22 months | Absent |
| 4 | F | 28 | Left temporo-occipital | Normal | Normal | Left inferior parietal lobe+precuneus | FCD Type I | 17 months | Decreased |
| 5 | M | 25 | Right occipital | Right temporo-occipital lobe lesion | Right temporo-occipital lobe hypometabolism | Right temporal | FCD Type II | 40 months | Absent |
| 6 | M | 20 | Right mesial temporal | Right mesial temporal | Right temporal mesial and lateral hypometabolism | Right temporal | Hippocampal sclerosis Type I | 44 months | Absent |
| 7 | M | 32 | Left temporal | Loss of cortical subcortical volume: Left temporo-central/ inferior temporal gyri all occipital lobe; parietal lobe posterior | Left temporo-occipito-parietal hypometabolism | Left inferior temporal gyrus+lateral temporo-occipital gyrus | Neurofibromatosis | 19 months | Absent |
| 8 | F | 12 | Left temporo-central | Normal | Normal | Left precentral/postcentral gyri+superior temporal gyrus, supramarginal gyrus | FCD Type II | 14 months | Absent |
| 9 | M | 23 | Left mesial temporal | Left anterior temporal signal increasing | Left temporal hypometabolism | Left Temporal | Hippocampal sclerosis Type I | 38 months | Absent |
| 10 | F | 28 | Right mesial temporal | Right temporal cortical organization disorder | Right temporal lateral+mesial hypometabolism | Right Temporal | Right mesial temporal sclerosis + FCD | 32 months | Absent |
| 11 | M | 17 | Left temporal | In right fusiform gyrus and parahippocampal gyrus, cortical organization disorder | Right mesial temporal hypometabolism | Right fusiform gyrus and inferior temporal gyrus | Pleomorphic xanthoastrocytoma | 35 months | Absent |
| 12 | F | 22 | Right mesial temporal | Right mesial temporal sclerosis | At the level of the pole, distinct right temporal lateral + mesial hypometabolism | Right mesial temporal | Hippocampal sclerosis+middle, inferior, superior, temporal gyri, FCD Type I | 24 months | Absent |
| 13 | M | 47 | Right temporal | Normal | In right frontobasal and frontoanterior sections, hypometabolism | Right superior middle temporal gyrus+angular gyrus | FCD Type II | 43 months | Decreased |
| 14 | F | 19 | Right temporal | Along the right fusiform gyrus and parahippocampal gyrus, thicker cortex than normal+right hippocampal sclerosis | Right mesial temporal hypometabolism | Right temporal | Ganglioglioma | 39 months | Absent |
| 15 | M | 5 | Right temporal | Right temporal pole and right inferior temporal gyrus localization FCD | Not done | Right temporal polectomy+ inferior and middle temporal gyri polectomy | FCD Type II | 53 months | Absent |

M = Male, F = Female, FCD = Focal cortical dysplasia

of the brain onto all of the points of a 3D grid. Every point whose activity is reformed is considered to be a potential source localization; therefore, a presumed number of sources is not necessary for the model, unlike dipole source modeling methods. In this method, the smoothest spatial distribution is selected by minimizing the Laplacian of weighted current sources. The assumption is that neighboring voxels should have a maximally similar electrical activity, such as the same orientation and activation. The significant feature of LORETA is that it facilitates inverse solution by providing spatial coefficients as input. This property is coming from the result of its time independency. To generate a combination of sources, it is enough to have one-time sample. Hence, we divided EEG activities into time windows for a solution, and these temporal windows were analyzed between the time of seizure onset and ~ 4 seconds later.

## Results

The LORETA map at the time of visible seizure onset, or appearing at the time of seizure semiology, was selected. The anatomical information obtained from the results of LORETA is given in Table 2.

### Patient classification according to scalp-EEG ictal patterns

The ESL group assessed using scalp EEG *ictal spike activity* included six patients. Of these, three patients (Patients 6, 11, and 15) were classified as having TLE, and the remaining three patients (Patients 1, 4, and 8) were classified as having ETLE.

The ESL group assessed using scalp EEG *rhythmic activity* included four patients. One patient (Patient 3) was classified as having ETLE, and the remaining patients (Patients 10, 12 and 13) were determined as having TLE.

The ESL group assessed using scalp EEG *paroxysmal fast activity* included four patients and all of them (Patients 2, 5, 9, and 14) had TLE.

The ESL group assessed using scalp EEG *obscured activity* included 1 patient and that person (Patients 7) was classified as having TLE.

### ESL results for the patients with MRI lesions

Nine of the postoperative patients with TLE were seizure-free. The epileptogenic zones that were obtained using LORETA method for ESL showed overlap with the resected area [see Figure 1].

### ESL results for the patients without MRI lesions

Two patients with TLE and four patients with ETLE were operated on after intracranial recordings were performed, because their MRIs were normal. For four of these patients, the epileptogenic zones obtained using LORETA corresponded to the resected area. LORETA method used in this study identified an area adjacent to the resected area as being related to the seizure in one patient with TLE [Figure 1, #13] and in one patient with ETLE [Figure 1, #4].

The ESL found using LORETA source model identified zones that were wider than the resected area for six patients.

### Concordance between Engel classification and ESL

The distribution of patients classified postoperatively according to the Engel classification of outcome is given in Table 3. Briefly, 11 patients with TLE, three with parietal lobe epilepsy (PLE), and one with frontal lobe epilepsy (FLE) were followed-up on over the course of at least 1 year postoperatively. All of these patients were seizure-free and belonged to Engel class I. After their operations, it was confirmed that the source localizations obtained using LORETA coincided with the same zone as the region that caused the seizures in these patients. The zone adjacent to the resected brain area was identified using LORETA for one patient with TLE and one patient with PLE who both had fewer seizures postoperatively.

### Surgery and histopathology

The resections identified the parietal lobe in three patients, the frontal lobe in one patient, and the temporal lobe for 11 of the 15 patients, and all of them were single-lobe resections. Histopathological analysis of the resected tissue showed focal cortical dysplasia (FCD) for eight cases, hippocampal sclerosis for two cases, both FCD and hippocampal sclerosis for two cases, ganglioglioma for one case, pleomorphic xanthoastrocytoma for one case, and neurofibromatosis for one case.

## Discussion

Comprehensive investigations are required preoperatively to determine the epileptogenic zone accurately. It is still difficult to determine epileptogenic zones for patients whose lesions cannot be detected with MRI or discordant imaging results using imaging methods. In this study, the zone determined using distinct types of scalp EEG ictal patterns was confirmed by comparisons between ESL and the resected area.

**Table 2: The anatomical information obtained from the results of ESL method for each participant**

| Patient | LORETA | Patient | LORETA | Patient | LORETA |
|---|---|---|---|---|---|
| 1 | Left superior frontal gyrus mesial face inferior/left cingulate gyrus intersections | 6 | Right temporal pole | 11 | Right mesial temporal posterior |
| 2 | Left temporal pole | 7 | Left temporal | 12 | Right temporal pole |
| 3 | Left supramarginal gyrus superior temporal gyrus mesial occipital lobe | 8 | Left precentral-postcentral gyrus distal 1/3 | 13 | Mesial temporal gyrus |
| 4 | Right superior occipital gyrus >Left superior occipital gyrus | 9 | Left temporal | 14 | Right temporal pole |
| 5 | Inferior temporal and fusiform gyrus | 10 | Right temporal | 15 | Right temporal |

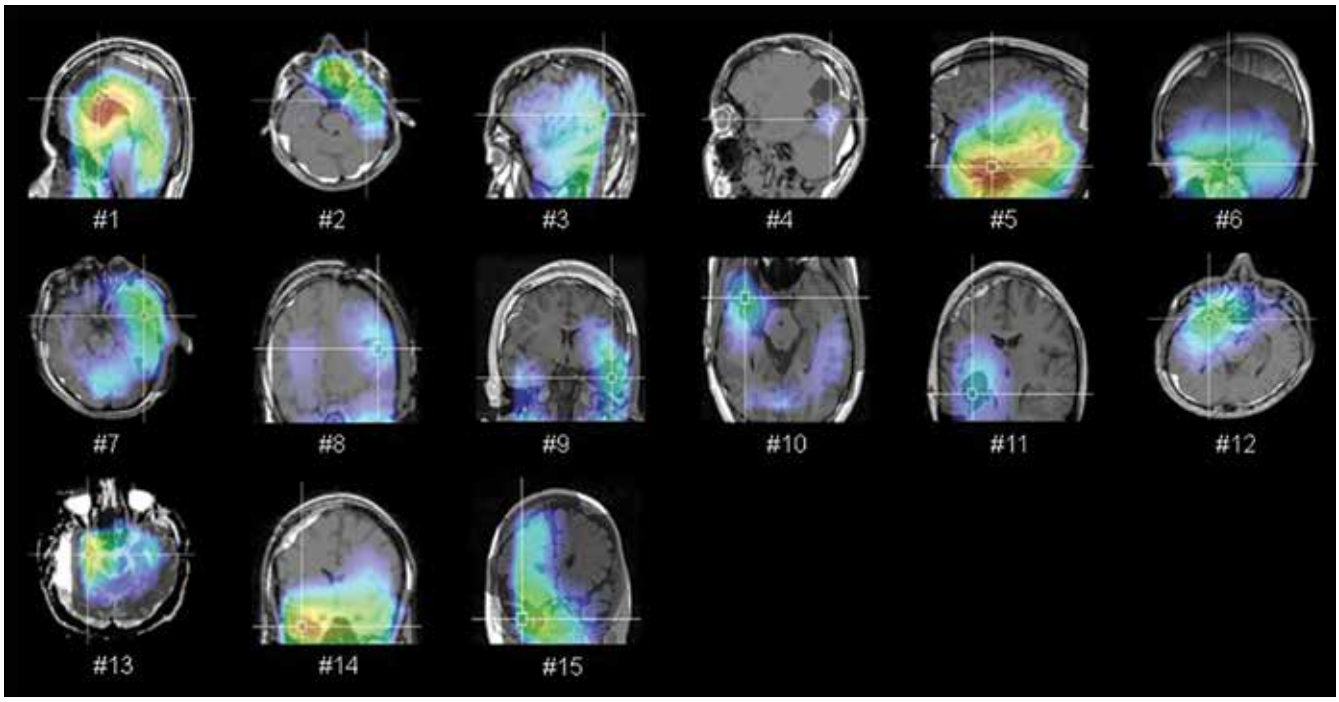


**Figure 1: The superposed images of LORETA source localization maps obtained by analyzing EEG ictal activity and postoperative MRI: Individual head model (dark gray color), including brain, skull and scalp was created using postoperative MRI scans for each patient. Electrode positions were localized, EEG analysis was performed, and electrodes were registered with individual head model. Finally, LORETA method was conducted to obtain ESL map and the highest activation area marked with crosshair. The ESL area we have found using LORETA method overlapped with brain resected area (black) except for the patients #4 and #13**

**Table 3: Patient distribution based on postoperative Engel outcome classification**

| Engel | I | III |
|---|---|---|
| Lobe | | |
| Temporal | 10 | 1 |
| Parietal | 2 | 1 |
| Frontal | 1 | – |

Methods based on solution of the inverse problem are used to obtain a physiologically meaningful source image although a unique solution is not possible to reach especially when physio-anatomical restrictions or boundary conditions are not very tight.[41] The reason why we chose LORETA among other available methods that use inverse solutions was that low-resolution methods can successfully estimate primary active zone though with a weak spatial resolution.[13,15,42,43] This method is a useful tool to reconstruct basic source configurations, but not huge amount of unconstricted sources in a determined region.[41] In addition, time independency is one of the most important characteristics of LORETA, so that localization of a combination of sources could be performed by just one time sample. Furthermore, no pre-assumption about the number of sources is needed in LORETA method. In the present study, confirmation was achieved by assessing the extent of overlap between the zone obtained by using LORETA and the area resected during surgery. Outcome of the surgery was also considered.

ESL was implemented on nine patients with lesions and six patients without lesions on their MRI. All of them had follow-up for at least one year. ESL results obtained using the patients' preoperative scalp-EEG data and postoperative MR images showed concordance with the resected brain region for 13 patients who were postoperatively seizure-free. In the remaining two patients, ESL identified a zone adjacent to the resected area, and this was interpreted as indicating that the epileptogenic zone had not been resected completely, as suggested by.[29] Those two patients did have seizures, though fewer, after their operations, supporting this interpretation. The current study supports a previous study which identified the epileptogenic zone accurately in eight of 10 patients with normal MRIs using ESL with the distributed source model, local autoregressive average (LAURA) method.[29] The main reason why a 88% accuracy rate could be achieved by ESL may be the utilization of each patient's individual digital MR images, and this is consistent with the results reported by Brodbeck and colleagues (2011).[30]

In our study, we were able to achieve an accurate ESL with LORETA for 13 of the 15 patients studied. The scalp ictal EEG of the remaining two patients (Patients 4 and 13) displayed ictal spiking and rhythmic activity. Ictal EEG records play a significant role for practical applications related with clinical matters like seizure propensity, seizure control, and drug-related neurotoxicity. Our findings support the results of Clemens and colleagues' study (2010),[44] which demonstrated that LORETA should be a beneficial tool for research on the matters mentioned above. This fact is supported by the insufficiency of other neuroimaging methods (magnetic resonance imaging methods, positron emission tomography) on this sort of problems.[44] The resected brain area was correctly

assigned in our study using LORETA for one postoperatively seizure-free patient whose scalp ictal EEG activity consisted of obscured activity. From this view point, our attempt seems to be a relatively successful one when compared with the study of Koessler and colleagues (2010),[19] who performed ESL using scalp EEG ictal data for nine patients (two of them with normal MRIs) with LORETA and assessed the accuracy of their ESL results by examining the determined epileptogenic zone using intracranial EEG recordings. Although they were able to identify the epileptogenic zone accurately for seven patients with abnormal MRI and determined accurately the area causing the seizures for one of the two patients with normal MRIs, they failed to do the same thing for the other patient whose scalp EEG ictal activity had consisted of obscured activity.

An area overlapping with but somewhat wider than the resected region was estimated to be epileptogenic using the ESL data obtained from LORETA for six patients. In three of these patients, it was observed that the scalp EEG was composed of spike activity. Of these three patients, two had rhythmic activity, and one had obscured activity in their scalp EEG. This can be interpreted as that the determined wide area is resulting from each possible current source localization that arises from the measured EEG's topographic representation on the surface of the scalp, as reported by.[45] In addition, it is suggested that distributed models are not sufficient to determine the epileptogenic zone when they are used alone, but they can provide valuable knowledge, especially in cases in which information regarding seizure propagation is needed. LORETA source model are more proficient in localization of widespread regions compared to localizing limited areas.

Michel *et al.* (2004a, b)[8,9] points out that using MRI scans of individuals is beneficial in determination of an epileptogenic zone with a single dominant focus, which was the case for our patients. Therefore, one reason why in our study the epileptogenic zone determined by using LORETA is concordant with the resected area for postoperatively seizure-free patients, may be because their individual MR data were used to construct the head model. From this point of view, our results are in line with those of[30] who used the patients' own MRI to construct the head model for ESL and reported their localization precision with a sensitivity of 84% and specificity of 88%.

In this study, histopathology of resected tissue from the patients revealed FCD and hippocampal sclerosis. An accurate ESL could be achieved by using LORETA despite these disparate histopathological results, suggesting that successful ESL is possible even in cases no histopathological information is available.

### Significance of the study

Based on verification using postoperative MR images of patients, it is demonstrated in this ESL study that accurate estimation of epileptogenic region is possible by employing the LORETA method. Our results suggest that the information obtained by means of LORETA can be used in planning surgery according to the type of epilepsy and its most likely sites in the individual patient. For clinicians who are in need of noninvasive methods based on advanced quantitative EEG that can accurately identify and localize the epileptogenic zone in higher number of candidates for surgery, the results of the present study are promising.

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### Conflicts of interest

There are no conflicts of interest.

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