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Localization of ictal onset zones in Lennox-Gastaut syndrome using directed transfer function method

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Abstract—**Neuroscientists are becoming interested in the application of computational EEG analysis to the identification of ictal onset zones, however, most studies have focused on the localization of ictal onset zones in focal epilepsy. The present study aimed to estimate the ictal onset zone of Lennox-Gastaut syndrome (LGS) with bilaterally synchronous epileptiform discharges from intracranial electroencephalography (iEEG) recordings using directional connectivity analysis. We analyzed ictal iEEG data acquired from three patients with LGS. To identify the ictal onset zones, we estimated the functional directional connectivity network among the intracerebral electrodes using the directed transfer function (DTF) method. The analysis results demonstrated that areas with high average outflow values corresponded well with the surgical resection areas identified using electrophysiologic data and conventional neuroimaging modalities. Our results suggest that the DTF analysis can be a useful auxiliary tool for determining surgical resection areas prior to epilepsy surgery in LGS patients.**

I. Introduction

PRECISE identification of ictal onset zones in patients with intractable drug-resistant epilepsy is of great importance for successful epilepsy surgery. To estimate ictal onset zones, various neurophysiologic and neuroimaging modalities have been utilized. However, the noninvasive imaging modalities have not been directly used to localize the surgical resection areas, but have been used as supplementary tools to determine the locations of intracranial EEG (iEEG) electrodes, because of the relatively limited spatial resolutions of these tools. Indeed, information obtained from iEEG recordings is regarded as the gold standard for presurgical evaluation prior to epilepsy surgery.

The ictal onset zones have been usually identified visually by well-experienced electroencephalographers. Recently, neuroscientists have become interested in the application of computational EEG analysis methods to the identification of ictal onset zones and epileptic networks. To identify ictal onset zones, various functional connectivity measures have been adopted. Among various indices to measure functional connectivity between neural signals, DTF has attracted the most attention as it can efficiently estimate causal interactions among multiple EEG signals in the frequency domain. Since Kaminski and Blinowska [1]'s first report in the early 1990s, DTF has been applied extensively to the analysis of epileptic networks. Series of studies have demonstrated that the DTF technique can be used to successfully identify ictal onset zones from iEEG recordings. Moreover, the DTF-based approach has been combined with EEG-based or electrocorticogram-based source localization methods [2], [3].

Despite extensive studies on DTF-based ictal onset zone localization, however, all of the previous studies have focused only on the localization of ictal onset zones in focal epilepsy. However, in some patients with generalized epilepsy such as Lennox-Gastaut syndrome (LGS), localization of ictal onset zones is also critical for surgical treatment. LGS is described as an epileptic syndrome with intractable, multiple seizure types including tonic, atonic, myoclonic and atypical absence seizures. Some patients with LGS have focal lesions that attribute to secondary generalized epileptic encephalopathy. Because of their generalized ictal iEEG discharges, however, surgical resection areas are usually determined based on their interictal characteristics on iEEG, with the help of advanced neuroimaging techniques. Recent studies reported successful outcomes of resective epilepsy surgery for children with LGS, despite abundant generalized and multiregional EEG abnormalities [4], [5]. However, additional refinement techniques to confirm the locations of ictal onset zones are still required. In the present study, we localized ictal onset zones in three LGS patients by applying the DTF method to ictal iEEG recordings obtained before epilepsy surgery and investigated the feasibility of using the DTF method for pre-surgical evaluation of LGS.

II. Patients and iEEG Recordings

Three pediatric patients with intractable LGS were included for the present study (Table I). All patients were evaluated for epilepsy surgery using various modalities including iEEG. All patients have been seizure-free after focal resective surgery conducted in Severance Hospital, Korea. Parents or guardians of all LGS patients were asked to provide a written consent that was approved by the Institutional Review Boards of Severance Hospital before their child's data were enrolled in the study.

The ictal iEEG recordings were obtained from a

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multichannel digital EEG acquisition system (Telefactor, Grass Technologies) at a sampling rate of 200 Hz. The locations of the silastic subdural grid and strip electrodes which are implanted on the cortical surface were determined based on the presurgical neuroimaging data. In each recording, 16 to 20 seizure events were observed per patient. Identification of the ictal onset times were determined by the electroencephalographers with the aid of video monitoring. Fig. 1 is an example of the ictal iEEG signals recorded at 104 subdural electrodes. Any pre-processing procedures were not applied to the raw signal except for baseline correction and 60 Hz notch filtering.

TABLE I
PATIENTS' INFORMATION

Patient Number	Age	Sex	No. ictal events	No. subdural electrodes
1	3	Male	20	104
2	2	Male	16	100
3	3	Male	19	116

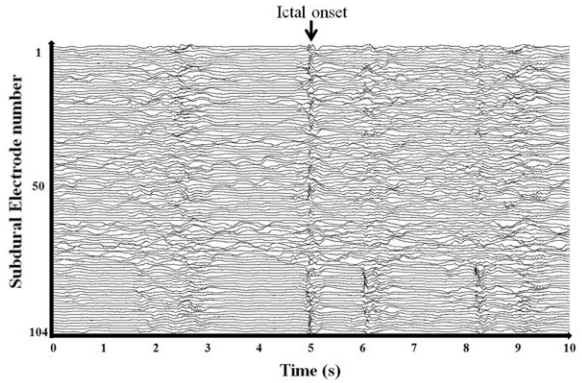

Fig. 1. An example of ictal iEEG recordings recorded from 104 subdural electrodes (patient 1).

III. DTF METHOD

iEEG recordings from three LGS patients were analyzed using the DTF method to localize the ictal onset zone [1], [6]. DTF is formulated in the framework of the multivariate autoregressive (MVAR) model [7]-[10], a multivariate process can be described as a data vector X of M source signals: $X(t) = (X_1(t), X_2(t), \ldots, X_M(t))^T$. The MVAR model can then be constructed as

$$X(t) = \sum_{n=1}^{p} A_n X(t-n) + E(t), \quad (1)$$

where $E(t)$ represents a vector composed of white noise values at time t, A_n is an $M \times M$ matrix composed of the model coefficients, and p is the model order. In the present study, the model order was determined by means of criteria derived using the Bayesian information criterion (BIC) [11]. The BIC generally penalizes free parameters more strongly than does the Akaike information criteria [8]. Average model orders for patients 1, 2, and 3 were 5.55 ± 1.01, 4.44 ± 1.09, and 8.05 ± 1.08, respectively. We also assured that slight changes in model order (± 1) did not influence the resultant DTF patterns. The MVAR model was then transformed into the frequency domain as follows:

$$X(f) = A^{-1}(f)E(f) = H(f)E(f), \quad (2)$$

where f denotes a specific frequency and the $H(f)$ matrix is the so-called transfer matrix, which is defined as

$$H(f) = A^{-1}(f) = \left(\sum_{n=0}^{P} A_n e^{-i2\pi fn\Delta t} \right)^{-1}, \quad A_0 = -I, \quad (3)$$

where I is an identity matrix.

The DTF was defined in terms of the elements of the transfer matrix H_{ij} as

$$\gamma^2_{ij}(f) = \frac{|H_{ij}(f)|^2}{\sum_{m=1}^{k} |H_{im}(f)|^2}, \quad (4)$$

where $\gamma_{ij}(f)$ denotes the ratio between inflow from signal j to signal i and all inflows to signal i, and k is the number of signals. The DTF ratio ranges from 0 to 1, with values close to 1 indicating that signal i is caused by signal j. In contrast, values close to 0 indicate that there is no information flow from signal j to signal i at a specific frequency.

We observed distinct increases in the spectral power around the ictal onset time in most iEEG channels. The frequency band that showed distinct changes in spectral power was very broad. Similar changes were observed in all ictal events of the three patients. Based on the time-frequency analysis, we determined the frequency band of interest (FOI) to be 8 – 50 Hz for all patients. We confirmed through several simulations that the bandwidth of FOI had a negligible influence on the DTF analysis results, even when the FOI was restricted to only the alpha frequency band (8 – 12 Hz).

We then evaluated the DTF values for each ictal event. Unlike partial epilepsy, the ictal activity in LGS does not last for seconds, of which the waveforms are similar to those of interictal spikes in partial epilepsy. Therefore, the ictal onset time was selected at the peak of the ictal wave. The analysis time window was determined to 800 time samples (4 sec) centered at each ictal onset time, considering the duration of the ictal events and the trade-off between accuracy and computational efficiency. We also confirmed that different window sizes ranging from 3.5 sec to 5 sec did not influence the resultant outflow patterns. The DTF values $\gamma_{ij}(f)$ were then averaged over the FOI (8 – 50 Hz in the present study), resulting in a single value, denoted as τ_{ij}, between a pair of signals i and j.

To quantify the extent to which an individual signal affects the generation of other signals, the averaged outflow of an i-th signal was evaluated as

$$OF_i = \frac{1}{k-1} \sum_{\substack{j=1 \\ j \neq 1}}^{k} \tau_{ji}, \quad (5)$$

where k is the number of signals. Zones with higher outflow values can be regarded as probable ictal onset zones. All of the above processes were performed using Matlab (ver. 7.8, Mathworks, Inc., USA).

After evaluating the outflow value for each iEEG signal, the distributions of the outflow values were illustrated on 3D brain images. The cortical surface model was generated from the individual T1-weighted MR images and the locations of the subdural electrodes were obtained from the individual CT images using CURRY6 (Compumedics, Inc., USA). The resultant outflow maps were generated using Matlab.

IV. Results

We first estimated the DTF values of the iEEG signals recorded from the three LGS patients, then overlayed the averaged outflow values defined in (5) on each patient's 3D anatomical images. The outflow maps corresponding to the averaged outflow values from each ictal event analyzed in the patient 1 are shown in Fig. 2. These results were normalized so that the electrode with the maximum activity in each analyzed ictal event had unit strength and were averaged across all of the analyzed ictal events in each patient (Fig. 3(b)).

In patient 1, the 3D outflow maps depicted in the first row of Fig. 3(b) consistently showed high outflow values around the right dorsolateral prefrontal cortex (DLPFC) for all ictal events; these areas coincide well with the surgical resection areas depicted in the first row of Fig. 3(a). Although some spurious or widespread outflow distributions were observed outside of the resection areas, the overall distributions were not very different from the common outflow patterns, and all of them overlapped with the resection areas.

The second row of Fig. 3(b) shows the distributions of the averaged outflow values of patient 2. In this patient, 16 ictal events acquired from 100 electrodes were analyzed. The outflow distributions observed in this patient showed the most consistent pattern among those of the three LGS patients considered in the present study, with a wide distribution over the superior DLPFC and premotor cortex. None of the events showed uncommon outflow distributions. A comparison of the outflow distributions with the surgical resection areas depicted in the second row of Fig. 3(a) clearly demonstrates that the anterior part of the outflow distribution overlapped with the resection areas. However, we confirmed after blinded analysis that the posterior part had been also identified as a primary ictal onset zone based on other presurgical evaluation methods but this region had been excluded from the final epilepsy surgery plan, as it might be associated with the patient's motor functions. Interestingly, the middle and the inferior temporal gyri included in the surgical resection areas were not identified as primary ictal onset zones in the present analysis. These results suggest that activity around the temporal lobe may be propagated from another region, although we have no way to test this hypothesis. In future studies, we intend to determine the accuracy of our approach by quantitatively comparing the present results with those from different imaging modalities.

The third row of Fig. 3(b) shows the distributions of the averaged outflow values for patient 3. In this patient, 19 ictal events recorded from 116 electrodes were analyzed. Although the high outflow distributions were not as distinct as those of patients 1 and 2, most maps showed high outflow values around the prefrontal cortex, and medial frontal eye fields, with fairly good overlap with the surgical resection areas depicted in the third row of Fig. 3(a).

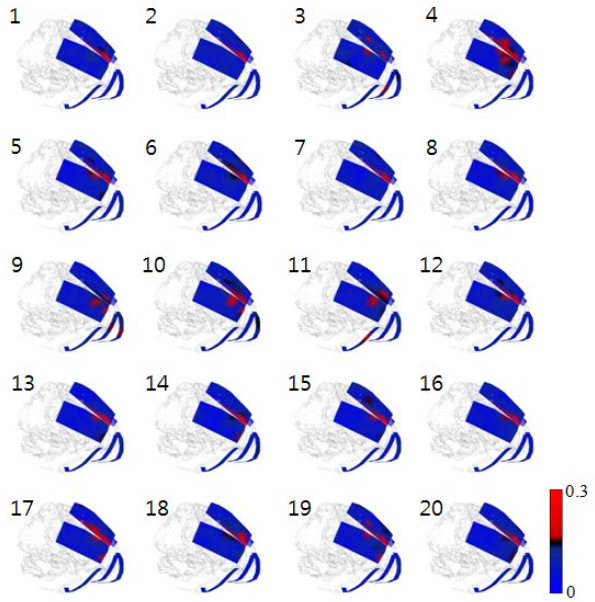

Fig. 2. 3D outflow maps of the DTF results for 20 ictal events in patient 1.

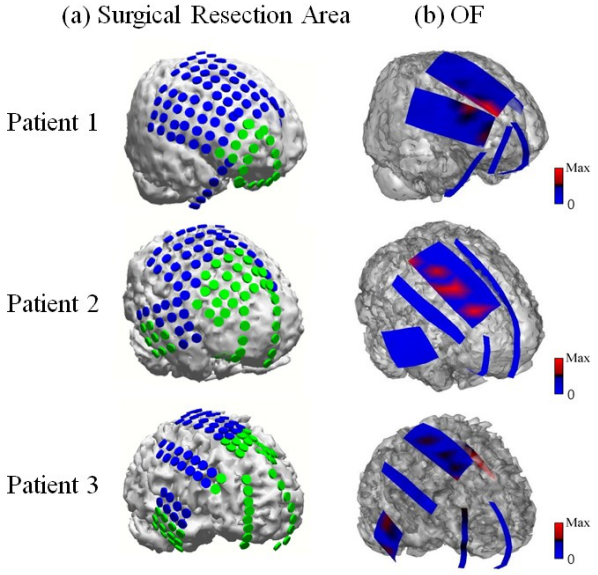

Fig. 3. (a) Surgical resection areas of three LGS patients. Circles indicate the subdural electrodes and green circles are the electrodes included in surgical resection areas of the patients; (b) Averaged outflow maps of the DTF analysis. Red areas indicate regions that had high outflow values. (All values are normalized to the maximum value.)

V. Discussion

In the present study, we applied the DTF technique to localize the ictal onset zones in LGS patients. The analysis results demonstrated that areas with high outflow values corresponded well with surgical resection areas identified by multiple neuroimaging modalities, suggesting that directional connectivity analysis can be used as an auxiliary tool to confirm the ictal onset zones identified using traditional neuroimaging modalities, as well as an alternative modality to determine the ictal onset zones of LGS patients.

The directional connectivity analysis that we performed in this study has an identical technical background to those of the previous studies [12]-[15]. However, contrary to the previous studies that attempted to localize the epileptogenic focus in patients with focal epilepsy, we used the DTF method to identify ictal onset zones in patients with secondary generalized epilepsy (LGS), demonstrating the feasibility of using the DTF method as a subsidiary neuroimaging modality for pre-surgical evaluation of LGS patients. In future studies, we hope to apply the present method to other types of intractable generalized epilepsies and also to investigate the accuracy of the localization of ictal onset zones by comparing the DTF results with results from existing neuroimaging modalities such as fMRI, PET, and SPECT.

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