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Localization of epileptogenic zones in Lennox–Gastaut syndrome (LGS) using graph theoretical analysis of ictal intracranial EEG: A preliminary investigation

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Abstract

Introduction: Precise localization of epileptogenic zones is essential for the successful surgical treatment of refractory epilepsy including Lennox–Gastaut syndrome (LGS). The surgical resection areas are generally determined by epileptologists based on diverse neuroimaging modalities; however, exact epileptogenic zones cannot be accurately localized in many patients with LGS using the conventional methods. Therefore, new reliable algorithms are still required for enhancing the success rate of the resective epilepsy surgery. In the present study, we introduce an approach to localize epileptogenic zones in LGS based on the graph theoretical analysis of ical intracranial EEG (iEEG). *Methods:* Four patients with LGS who became seizure-free after the resective epilepsy surgery were selected. Before the surgery, their epileptogenic zones were delineated using EEG, iEEG, and several conventional imaging modalities. Phase locking value (PLV) analysis was applied to construct functional connectivity networks during ictal events, and then several graph theoretical indices including betweenness centrality (BC) were evaluated for each iEEG sensor to find the primary hubs of the ictal epileptic network. The graph theoretical index values were then overlaid on 3D individual cortical surface. *Results:* The iEEG channels with high BC values coincided well with the surgical resection areas. Among various graph theoretical measures such as local efficiency, participation coefficient, and eigenvector centrality, only BC showed fair correspondence with the surgical resection areas. *Conclusions:* The primary hubs in the ictal epileptic networks coincided well with areas of surgical resection in LGS patients with successful surgical outcomes. This observation warrants further studies to determine if the graph theoretical network analysis of ictal iEEG recordings can serve as a new auxiliary tool to localize epileptogenic zones in LGS.

Keywords: Epileptogenic zone; Intracranial electroencephalography (iEEG); Lennox–Gastaut syndrome (LGS); Secondary generalized epilepsy; Phase locking value (PLV); Graph theory; Betweenness centrality

1. Introduction

For the successful surgical treatment of refractory epilepsies, locations of epileptogenic zones need to be precisely localized [1]. In contemporary, epileptogenic zones are localized based on various diagnostic tools,

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such as multiple neuroimaging modalities and seizure semiology. Nevertheless, in 20–30% of focal epilepsy patients, these tools still cannot exactly localize the epileptogenic zones [1–4]. Therefore, more diagnostic tools need to be introduced to facilitate higher success rate of epileptic surgery.

In spite of the high risks such as infection, increased intracerebral pressure, and venous infarction, intracranial electroencephalography (iEEG) recorded using subdural grid or depth electrodes has been regarded as a gold standard for determining the resection margin in epileptic surgery due to its higher signal-to-noise ratio (SNR) compared to scalp EEG [5]. Indeed, traditional surgical planning mainly relied upon visual inspection of iEEG recordings by experienced epileptologists; however, removal of epileptogenic zones identified with a visual inspection of iEEG does not always guarantee a favorable surgical outcome [6,7] because it is often difficult to distinguish ictal epileptogenic zones from irritative zones activated by propagation through visual inspection of ictal epileptiform activities.

Recently, various computational iEEG analysis methods have been introduced as a means of confirming visual inspection results and assisting in the final decision on surgical resection areas. For example, specific spectral patterns, relative powers, local hypersynchronization, and high frequency oscillations can be used as potential markers to identify epileptogenic zones [8–10]. Functional connectivity measures can also be used for the localization of epileptogenic zones. For instances, stochastic qualifiers [11] and directed transfer functions (DTFs) [12–16] have shown that functional connectivity-based measures could effectively identify epileptogenic zones that could not be readily identified via visual inspection. However, despite these extensive studies, most studies have focused only on the localization of epileptogenic zones in focal epilepsy. Only a few studies have attempted to apply computational iEEG analyses to the localization of epileptogenic zones in secondary generalized epilepsy [17,18]. In general, localization of epileptogenic zones in secondary generalized epilepsy is more difficult than in focal epilepsy, due to its generalized ictal epileptiform discharges. Therefore, one of the challenges remaining in this field has been the precise localization of epileptogenic zones in secondary generalized epilepsy. In the present study, Lennox–Gastaut syndrome (LGS) was selected as the target secondary generalized epilepsy type because it has been recently reported that some patients diagnosed with LGS can be treated through resective epilepsy surgery, but localization of epileptogenic zones via neuroimaging studies and visual inspection of ictal iEEG recordings is generally difficult due to the inconsistent neuroimaging results and highly generalized ictal epileptiform discharges.

Most patients diagnosed with LGS are preschool age children [19] and numerically 4% of all childhood epilepsy patients are suffering from LGS [20]. The LGS patients are almost medically refractory [21] and the 50–98% of the LGS patients still remain having more than 50% of seizures after antiepileptic drug treatments [22–25]. Some patients with LGS have focal lesions that attribute to secondary generalized epileptic encephalopathy. However, because of their generalized ictal iEEG discharges, surgical resection areas are generally determined based on their interictal iEEG characteristics, with the help of functional neuroimaging techniques. Recent studies reported successful outcomes of resective epilepsy surgery for some children with LGS, despite abundant generalized and multiregional EEG abnormalities [26]. Despite these conventional modalities, it is still difficult to correctly localize ictal epileptogenic zones in patients with LGS with abundant ictal/interictal generalized epileptiform discharges. Therefore, there is great demand for additional refinement techniques to confirm epileptogenic zones in LGS [26].

In the present study, we introduce a new approach for localizing epileptogenic zones of patients with LGS. We first evaluated functional connectivity networks during ictal events using phase locking value (PLV) analysis. Then, the betweenness centrality index, a kind of graph theoretical measures that can find hubs of given networks [27], was computed for each iEEG electrode. Two previous studies on the localization of epileptogenic zones in focal epilepsies also identified hubs in directed epileptic networks [28,29]; however, our approach differs from the previous ones in that the epileptic network was constructed using a phase synchronization measure (PLV) as well as the target epilepsy was not the focal epilepsy but the secondary generalized epilepsy. Our proposed approach was applied to four patients who became seizure-free after resective epilepsy surgery, with the aim to evaluate whether our approach can be potentially used as an auxiliary tool for the pre-surgical evaluation of patients with LGS.

2. Methods

2.1. Patients

Among 27 pediatric patients who had LGS and underwent resective epilepsy surgery during 2001–2007 at Severance Children's Hospital of Korea, 16 patients have been seizure-free since surgery. Among the seizure-free patients, four patients without cerebral infarctions or progressive underlying metabolic diseases or chromosomal anomalies were selected. The following five screening criteria were used to select the analysis datasets: (1) previously, patients had experienced multiple types of seizures like atypical absence, atonic, tonic and generalized tonic clonic seizures; (2) up to 30% of preoperative epileptiform discharges were typical EEG findings of LGS, generalized slow sharp and waves

and/or generalized paroxysmal fast activities with slow and disorganized background; (3) normal or nearly normal brain MRI findings without definite brain lesions including cerebral infarctions, progressive cortical atrophy or malformation of cortical development; (4) neuroimaging was not very helpful in localizing the epileptogenic area; and (5) completely seizure-free without any questionable episodes after surgery. Patients who did not satisfy all the above criteria were excluded from the study and the analyses were applied only to the selected patients' iEEG datasets. Table 1 summarizes the successfully operated patients' characteristics and demographic data. Parents or guardians of all enrolled patients provided written consent, and the study protocol was approved by the Institutional Review Board of Yonsei University Severance Hospital, Korea.

As summarized in Table 1, the four successfully operated patients commonly underwent right frontal and/or right temporal lobectomy especially two patients had surgery twice. After the surgery, they have been free of seizures for at least 4.3 years without medication. Since all patients obtained long-term seizure-free outcome, it is feasible to assume that the resection areas sufficiently contained the true epileptogenic zones. Before the surgery, all subjects were examined using a video-EEG monitoring system with electrodes placed according to the international 10–20 system to define the semiology of habitual seizures and to identify epileptogenic foci. Epileptogenic zones were delineated primarily through interpretation of EEG data. Other imaging modalities such as MRI, PET, and SPECT were used to reinforce these findings. iEEG monitoring using subdural electrodes was also used to determine margins for surgical resection. Preoperative and intraoperative functional mapping and intraoperative electrocorticography were also performed when necessary [26,30].

The surgical area was defined based on the clinical, neuroimaging, and electrophysiological results as summarized in Table 1. The resection margin for epilepsy of neocortical origin was defined by: (1) the presence of a discrete lesion on MRI and functional neuroimages compatible with ictal or interictal iEEG; (2) various interictal intracranial EEG findings, including more than three repetitive spikes per second, runs of repetitive spike and slow wave discharges, localized or spindle-shaped fast activities and electrodecremental fast activities; and

Table 1
Demographics and characteristics of patients with LGS.

Patient no.	1	2	3	4
Age at surgery	2 years	17 years	3 years	3 years
Sex	Male	Male	Male	Male
Age at first epilepsy development	5 months	12 years	7 months	18 months
Main seizure type	Head drops and atypical absences	Generalized tonic seizures of both arms	Generalized tonic spasms and head drops	Generalized tonic spasms and staring spells
MRI	Blurring of the gray–white matter interface on the right frontal lobe	Blurring of the gray–white matter interface on right frontal lobe	Normal	Suspicious but not definite cortical thickening on the right frontal lobe
FDG-PET	Normal	Hypometabolism on right frontal lobe	Normal	Focal hypometabolism on right frontal lobe
Ictal SPECT	Unsuccessful	Unsuccessful	Lateralized consistently to the right frontotemporal area	Lateralized consistently to the right frontotemporal area
Video-EEG	Right frontal area	Right frontal area	Right frontotemporal area	Right frontotemporal area
Surgery	(Once) Right frontal and right anterior temporal lobectomy	(Once) Right frontal lobectomy	(Twice) (1) right frontal lobectomy, (2) posterior margin of the pre-resection site	(Twice) (1st) right frontal lobectomy, (2nd) right inferior frontal gyrus & right temporal lobectomy
Outcome	Seizure-free (7.6 years)	Seizure-free (6.7 years)	Seizure-free (4.4 years)	Seizure-free (4.3 years)
Pathologic result	Focal cortical dysplasia	Focal cortical dysplasia	Focal cortical dysplasia	Focal cortical dysplasia
EEG after operation	Nearly normalized background activities with only occasional multifocal sharp waves	Nearly normalized background activities and no epileptiform discharge	Nearly normalized background activities and no epileptiform discharge	Nearly normalized background activities and no epileptiform discharge
No. subdural electrodes	100	120	104	116
No. ictal events in iEEG recordings	16	19	20	19

(3) the absence of an eloquent cortex. The diagnosis and classification of pathologic cortical dysplasia (CD) was made according to the system described by Palmini et al. [31].

2.2. iEEG data acquisition

Ictal iEEG data were recorded using a 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 were determined based on multiple neuroimaging data as described in the previous section. The recorded iEEG data were reviewed by an epileptologist, and 16–20 seizures were observed in each subject (see Table 1). Ictal onset times were identified visually by the epileptologist with the aid of video monitoring. Fig. 1 shows an example of the ictal iEEG data recorded from a patient (Patient 3). No specific pre-processing procedures except for baseline correction and 60 Hz notch filtering were applied to the raw iEEG data.

2.3. Phase locking value analysis on ictal iEEG data

We computed phase locking value (PLV) between all the possible pairs of recorded ictal iEEG signals, which is a well-known index to measure phase synchronization between two signals recorded from two different electrode sites in the same time interval and frequency band [32]. The PLV value ranges from 0 to 1, when the value close to 1 represents that two signals are synchronized with a constant time lag and the value close to 0 represents that the two signals are temporally independent with each other. Before calculating the PLV, the ictal iEEG data were segmented into 2-s epochs around the seizure onset time, considering the short duration of the ictal period (see Fig. 1) [17–18]. We used alpha frequency band for the PLV analysis as in our previous study [18] as all patients showed distinct spectral changes in alpha band. We confirmed that the slight changes in the frequency band (below 20 Hz) did not significantly affect the analysis results, but the results were changed to some extent when the frequency of interest was set to be higher than 20 Hz.

2.4. Graph theoretical analysis of epileptic network

We applied various graph theoretical measures such as betweenness centrality (BC) [27–29], local efficiency [33], participation coefficient [34], and eigenvector centrality [35], to find the primary hub nodes that play central roles in forming the ictal epileptic networks.

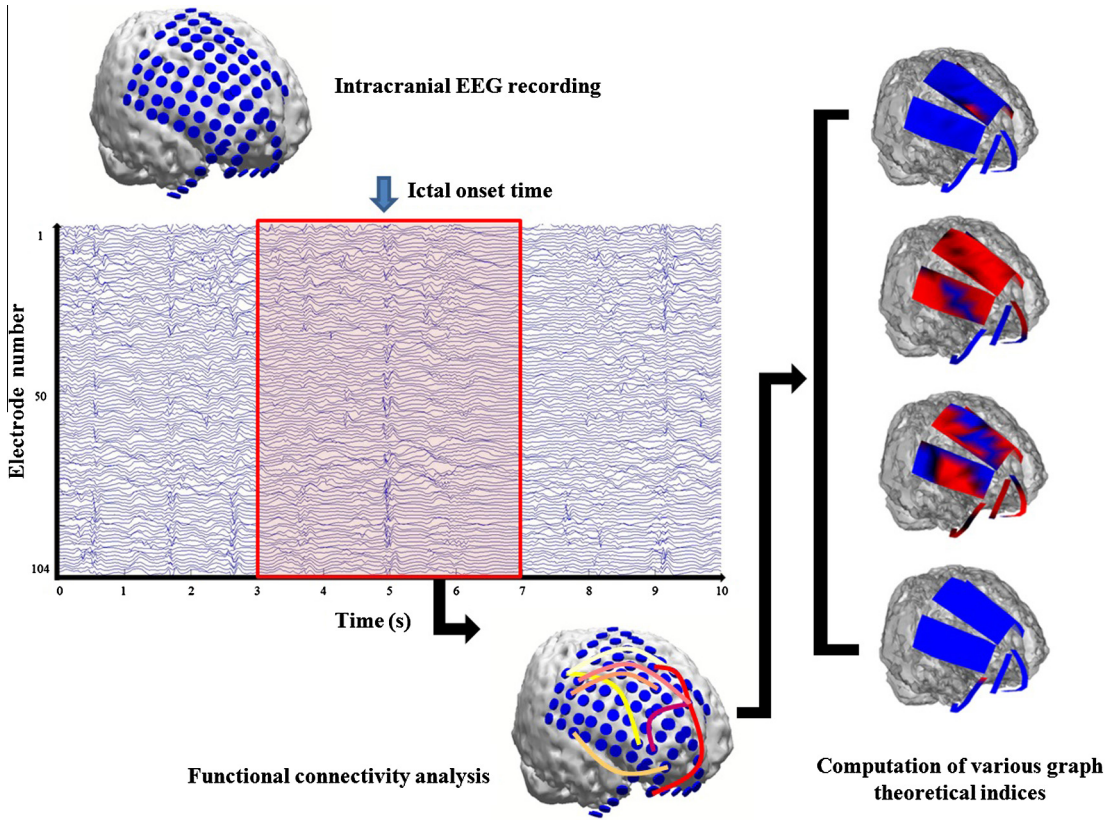

Fig. 1. A schematic illustration of the study procedures. First, a time segment containing the time of ictal onset was selected from the iEEG recordings. A functional connectivity network was then evaluated using the PLV analysis. Various graph theoretical measures were evaluated for each node and the resultant distribution was overlaid on the individual cortical surface.

More detailed information on the above indices can be found in a review paper [36], and the equations used for the calculation of graph theoretical indices are summarized well in another review paper [37].

After calculating the index values of each electrode for each trial, the index values were averaged across all trials. Then, the distribution of the averaged indices was overlaid on 3D cortical surface images (see Fig. 1). The cortical surface models of the LGS patients were generated from the individual T1-weighted MR images using CURRY6 for Windows (Compumedics, Inc., USA). The T1-weighted MR images were acquired from a commercial 3.0-T MRI machine (Achieva 3.0T Release 2.5.3.3, Philips, USA) using a ultrafast gradient echo T1-weighted 3D coronal sequence. The locations of the subdural electrodes were obtained from individual CT images and were semi-automatically registered on the segmented cortical surface model using the same software. The resultant distribution maps were generated using Matlab 2009a (Mathworks, Inc., USA). In the distribution maps, electrodes with higher index values were regarded as probable epileptogenic zones. Fig. 1 shows the schematic diagram of the analysis procedure. All the analyses were performed blindly without knowing any clinical information on the patients, and then the analysis results were compared with the actual surgical resection areas.

3. Results

Fig. 2 shows the distributions of BC values overlaid on the sensor surface as well as the surgical resection areas marked in green color. In the first patient's result, most hubs identified by the BC distribution coincided well with the surgical resection areas, the right temporal lobe and right frontal lobe. It is noteworthy that two hubs located near the right anterior temporal lobe were not identified in our previous studies that used the same patient's iEEG dataset [17,18].

In the second patient's result, most primary network hubs identified by the BC distribution coincided with the surgical resection area, but one electrode outside the surgical resection areas, located around the primary sensory-motor cortex, showed a higher BC value. This localized hub might reflect the patient's seizure semiology, which was identified generalized tonic seizure, vocalization with both arms tonic or automatic behavior.

In case of the third patient, who underwent two successive epileptic surgeries – resection of right dorsolateral prefrontal cortex (DLPFC) in the first surgery and resection of the posterior margin of the pre-resection site in the second surgery. As the result of the BC analysis, three hubs were identified as probable epileptogenic zones. Two hubs were located at the right and mesial DLPFC, respectively, which coincided with the surgical resection areas. The location of the remaining hub was located outside the surgical resection areas, which was the right medial premotor cortex (Brodmann area 6). Considering that he suffered from generalized tonic, myoclonic and head drops during seizure, this hub location might be also related with the patient's seizure semiology.

The last patient had generalized tonic, myoclonic and staring spells seizures. The patient underwent epileptic surgery twice, first resective surgery in right frontal lobe and second resective surgery in right inferior frontal gyrus and right temporal lobe. The patient had network hubs in the right primary motor cortex (Brodmann area 4), the right anterior prefrontal cortex (Brodmann area 10), and the right medial frontal eye field (Brodmann area 8), which corresponded well with the surgically removed areas.

We also applied other graph theoretical measures (local efficiency, participation coefficient, and eigenvector centrality) to the same iEEG data, but could not

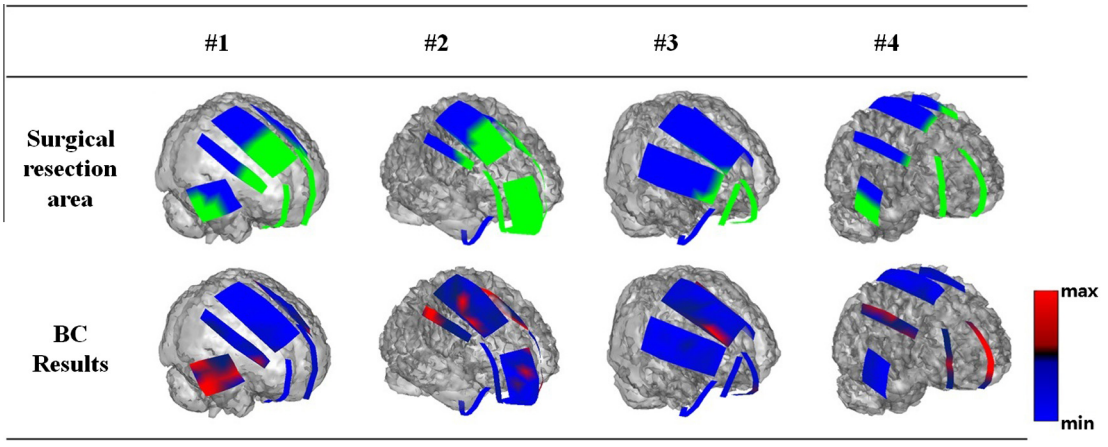

Fig. 2. Distributions of the betweenness centrality index of patients with LGS. In the first row, green color indicates the surgical resection areas determined by epileptologists. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

obtain any meaningful results that can be potentially used for the declination of the ictal epileptogenicity of the patients with LGS (see Fig. 3).

4. Discussions

LGS is characterized by different types of generalized seizures such as tonic, atonic, and absence seizures. These types of seizures are difficult to be treated by anti-epileptic drugs, and thus some LGS patients with focal lesions that attribute to secondary generalized epileptic encephalopathy need surgical treatments. However, despite the development of neuroimaging technologies, it is difficult to precisely localize ictal epileptogenic zones in patients with LGS due to the abundant ictal/interictal generalized epileptiform discharges. In our previous studies, we introduced two computational iEEG analysis methods, DTF analysis and time delay analysis, for the localization of epileptogenic zones in patients with LGS, and showed that the computational iEEG analyses could be potential auxiliary tools for the presurgical evaluation of LGS [17,18]. Nevertheless, introduction of new iEEG analysis methods is still needed to confirm epileptogenic zones in LGS because the previous methods did not result in consistent estimates of epileptogenic foci in all patients.

In the present study, we localized epileptogenic zones by searching hub nodes in ictal epileptic network constructed using functional connectivity analysis of ictal iEEG data. We hypothesized that the hubs of the epileptic network should be highly synchronized with other nodes (irritative zones activated by propagation) during the ictal event. We computed the functional connectivity network using a synchronization measure based on the Dominguez et al.'s study which reported increased phase synchronization in electrodes near epileptogenic zones during generalized absence and tonic seizures [38]. As there would be a certain amount of time delay between the signals of an epileptogenic zone and an irritative zone [17], the epileptic network was constructed using PLV, which can measure the consistency of phase difference instead of the phase difference itself. Among various graph theoretical indices applied to the epileptic networks, only the BC measure could find the central hubs of the network relatively more accurately. The hub nodes identified by our approach coincided fairly well with the surgically resected areas of LGS patients who became seizure free after the epileptic surgery. Interestingly, unlike our previous approaches [17,18], the results of the present analyses could identify some regions that were related to the patients' specific cortical regions involving in their seizure semiology. Considering that the conventional neuroimaging modalities provided rather crude estimates of epileptogenic zones in secondary generalized epilepsy, as is easily observed in Table 1, it is expected that the localization of epileptogenic zones using ictal iEEG would serve as an auxiliary imaging modality for pre-surgical evaluation. In addition, considering that various methods for localizing epileptogenic zones provided different localization results in each patient, a proper combination of these methods might provide an opportunity for attaining a better accuracy in presurgical evaluation. Therefore, it is still required to explore new indices for the localization of epileptogenic zones in LGS. Moreover, one of the promising topics we hope to explore in future studies is the

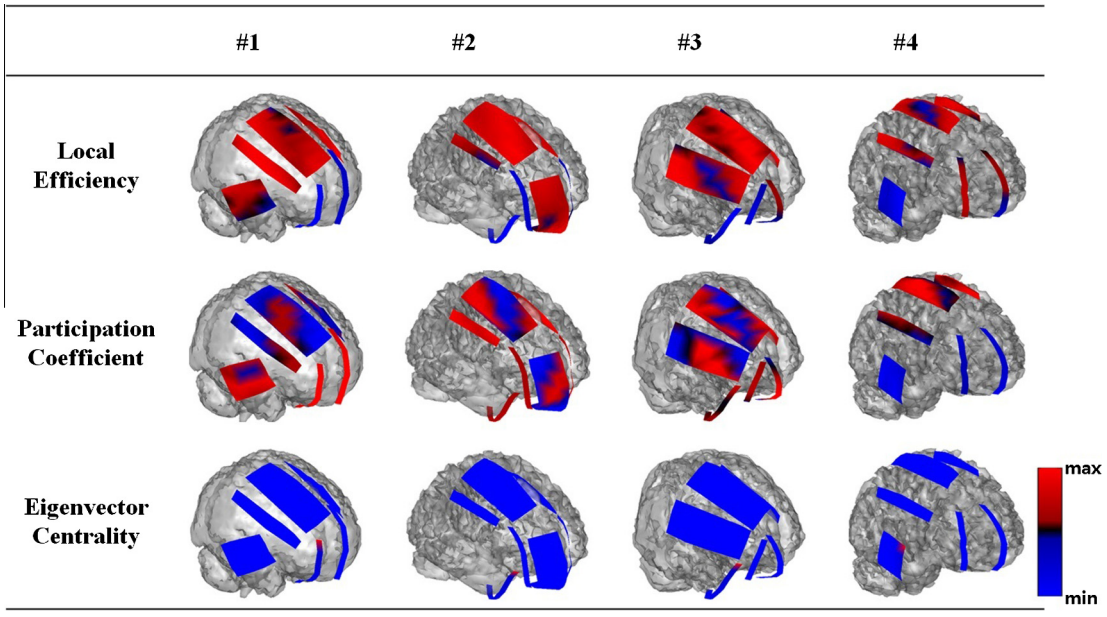

Fig. 3. Distributions of local efficiency (first row), participation coefficient (second row), and eigenvector centrality (third row) values of patients with LGS.

quantitative comparison of performances among various iEEG analysis methods for the localization of epileptogenic zones, with the aim of demonstrating the usefulness of each iEEG analysis method and determining the most reliable method.

Before the present study, Wilke et al. and Varotto et al. also localized probable epileptogenic regions by searching primary hubs in epileptic network during seizure [28,29]. They showed that the primary hubs in the epileptic network coincide fairly well with the surgical resection areas, but they applied the graph theoretical approach to iEEG data acquired from patients with focal epilepsy. In the present study, we applied various graph theoretical measures to patients with LGS, which is a representative type of secondary generalized epilepsy, for the first time. We have demonstrated that the BC index evaluated for the ictal epileptic network could be a potential indicator of the epileptogenic zones in LGS.

The other three graph theoretical indices, local efficiency, participation coefficient, and eigenvector centrality, were also applied to find epileptogenic zones in LGS, but unfortunately they did not result in positive results. Among the three indices, the local efficiency is a measure of segregation, which evaluates the contribution of a node to the network efficiency [37]. Our results demonstrated that the local efficiency values did not show distinct differences among channels, suggesting that the epileptogenic zones might not be directly associated with the efficiency of the epileptic network. The other two indices, participation coefficient and eigenvector centrality, are measures of centrality (or hub) [38]. Participation coefficient is known as a measure of diversity of intermodular connections of individual nodes. The widespread distribution of the participation coefficient might suggest that the epileptic functional network in LGS might not have well-defined modular structures but have a dispersed structure. Eigenvector centrality is an index similar to BC [38], but it showed more focalized distributions than BC. It is well-known that different centrality indices result in different value distributions for the same graph. It is generally known that the eigenvector centrality provides more focalized value distribution than BC (for example, refer to the simulation results in http://en.wikipedia.org/wiki/File:Centrality.svg), and thus it might be more adequate for the localization of epileptogenic zones in focal epilepsy with a small number of sparse epileptic foci.

There are some limitations in our study. First, although a large number of intracranial electrodes were attached on probable epileptogenic areas that were determined by various neuroimaging modalities, it is still possible that the cortical areas where electrodes were not placed may potentially influence the results of the analysis. This issue needs to be further explored in future studies based on computer simulations. Second, the number of patients and seizure events were small. Only four seizure-free patients were enrolled in this study as it was difficult to find patients with LGS who had undergone successful epilepsy surgery and did not have cerebral infarctions or progressive underlying metabolic diseases. Third, although we did not have any selection biases, the four selected cases commonly showed resected areas in right frontal and temporal lobes. Therefore, it is difficult to generalize our study results to other cases with seizure onsets in other regions. Considering all these limitations in the collected data, the present results should be interpreted with caution, and considered as preliminary data to introduce the methodologies for future studies with a larger scale. In future studies, more extensive computational iEEG analyses should be performed to quantitatively compare the performances of various neuroimaging modalities. In addition to the current analyses applied only to LGS patients with successful surgical outcomes, it would be interesting to apply this study approach to a larger sample of patients who were not seizure-free after the resective epilepsy surgery. This would make it possible to investigate whether the epileptogenic zones localized by our approach were not completely removed during epilepsy surgery in patients with unfavorable surgical outcomes. Apart from these retrospective studies, prospective studies should be considered as the final goal of this series of studies in order to further verify that the removal of central hubs identified using our approach can lead to a complete seizure control.

In the future studies, we will also analyze temporal change of epileptic network in patients with LGS using the present approach. As connectivity patterns vary from interictal state to ictal state according to a previous study [28], tracking the locations of the network hubs might provide an interesting feature that may elucidate the epileptogenesis of LGS.

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