Seizure 33 (2015) 1–7

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The causal epileptic network identifies the primary epileptogenic zone in Lennox–Gastaut syndrome

Yun Jung Hur [a], Heung Dong Kim [b,*]

[a] Department of Pediatrics, Haeundae Paik Hospital, Inje University College of Medicine, Pusan, Republic of Korea
[b] Department of Pediatrics, Pediatric Epilepsy Clinic, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 8 October 2014
Received in revised form 6 October 2015
Accepted 7 October 2015

Keywords:
Lennox–Gastaut syndrome
Generalized sharp and wave discharge
Direct directed transfer function
Resective surgery

ABSTRACT

Purpose: Lennox–Gastaut syndrome (LGS) can be successfully treated by resective surgery in patients with a primary epileptogenic zone. This study aimed to identify the primary epileptogenic zone based on the causal epileptic network using direct directed transfer function (dDTF) analysis.
Methods: We reviewed the dDTF findings for generalized sharp and wave discharges (GSW) from the preoperative electroencephalography (EEG) of 12 LGS patients (group A) with unilateral focal pathology who were successfully treated with resective surgery. These findings were compared with preoperative dDTF findings for the GSW from 15 LGS patients with bilateral non-resectable pathology (group B) who exhibited persistent bilateral independent diffuse sharp and wave discharges, even after corpus callosotomy.
Results: The dDTF analysis of the GSW revealed concordant findings of localization or lateralization with the primary epileptogenic zone in 83.3% (10/12 cases) of group A patients and bilateral or multifocal localization in 93.3% (14/15) of group B patients ($p < 0.01$). The regions identified by dDTF analysis were included in the resected areas of all patients in group A, and complete matches of the resected areas without other foci were observed in 7 patients (58.3%) in group A. The region of GSW most frequently identified by dDTF analysis was the frontal area, which was identified in 91.7% (11/12) of group A and in 100% of group B, while extra-frontal areas were identified in 36.1% and 24.5% of groups A and B, respectively.
Conclusions: The dDTF analysis of GSW could provide additional information to identify resective surgery candidates for patients with LGS.

1. Introduction

Lennox–Gastaut syndrome (LGS) is one of the most intractable epilepsies and is characterized by multiple types of seizures, electroencephalographic (EEG) characteristics, such as generalized slow sharp and wave discharges and generalized paroxysmal fast activities, and progressive mental retardation. Generalized sharp and wave discharges (GSW) with bilateral synchronization in a secondary generalized epileptic encephalopathy, such as LGS, can originate from the primary epileptogenic zone through the transcallosal pathway [1–3]. Although resective surgery of the primary epileptogenic zone results in a seizure-free surgical outcome in 59.2% of patients, the GSW often fail to reveal the primary epileptogenic zone if they are not accompanied by the types of focal EEG features that have been described in previous studies [2,3].

GSW display bilateral synchronization of the epileptogenic discharges and reflect the complex sum of all source activities, normal brain activities and noise via the EEG spatial filter. It is difficult to identify the primary epileptogenic zone by analyzing the GSW, even though many computational analyses have been developed [4–7]. In a GSW analysis, a source analysis using dipole modeling usually reveals a cluster of sources in the medial or lateral frontal, frontal polar and orbito-frontal areas [8,9]. However, these methods cannot indicate the directionality or causality of the combined data from multiple sources that contribute to the GSW. Therefore, we used direct directed transfer function (dDTF) to analyze the GSW to determine the directionality and causality of the sources and reviewed the evidence that identified the primary epileptogenic zone in LGS.

* Corresponding author at: Yonsei University College of Medicine, 134, Shinchondong, Seodaemun-gu, Seoul 120-752, Republic of Korea.
Tel.: +82 2 2228 2061; fax: +82 2 393 9118.
E-mail address: hdkimmd@yuhs.ac (H.D. Kim).

http://dx.doi.org/10.1016/j.seizure.2015.10.001
1059-1311/

2. Materials and methods

2.1. Patients

All patients met the inclusion criteria for LGS. The patients all had multiple types of seizures, including generalized tonic or tonic–clonic seizures, myoclonic seizures and atonic seizures, generalized slow sharp and wave discharges and generalized paroxysmal fast activities on EEG and mental retardation. We enrolled 12 LGS patients with a primary epileptogenic zone (group A) who attained a complete seizure-free outcome after resective surgery of the underlying pathological region. All patients underwent a pre-surgical evaluation, which included clinical characterization, video-EEG monitoring, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET). EEG features that indicated the primary epileptogenic zone included focal slow waves, localized paroxysmal fast activity, focal ictal discharge, unilateral absence of the sleep spindle and focal amplitude attenuation, as well as GSW with prominent lateralization or localization, as shown in a previous study [2]. Exclusion criteria for our study included prior brain surgery or other procedures before surgical treatment that could cause electrical or spatial distortion and the occurrence of seizure relapse during the follow-up periods. Surgical outcomes were determined based on the Engel classification during follow-up visits at an outpatient clinic [10]. We also selected 15 patients who exhibited persistent bilateral independent diffuse sharp and wave discharges in the postoperative EEG after complete corpus callosotomy (group B) as a comparison group for the dDTF findings of the GSW. The neuropathological findings for the resected areas were reviewed by an experienced neuropathologist [11]. The clinical differences between group A and group B were not statistically significant except for the focal evidence for each modality, the method of surgical treatment and the surgical outcome (Table 1).

We analyzed the GSW on the preoperative EEG and identified the primary epileptogenic zone using a dDTF-based multivariate autoregressive (MVAR) method. We evaluated the differences in the epileptic network of the GSW between the two groups. This study was approved by the Institutional Review Board, and all data analyses were performed without patient identifiers.

2.2. Data acquisition and source localization

Video-EEG monitoring before surgical treatment was conducted for 48 h using a digital EEG acquisition system (Grass Telefactor, Astro-Med Inc., West Warwick, RI, USA). A total of 22 electrodes were placed on the scalp in accordance with the international 10–20 system, and data were recorded at a sampling rate of 200 Hz and a band pass width of 0.5–70 Hz. The EEG recordings were interpreted by two epileptologists to identify the EEG characteristics that corresponded with LGS. We obtained 10-min EEG recordings for both the sleep and awake states using average reference. After we defined a GSW as an event, we marked its peak amplitude at the electrode on the frontal vertex, which was set as time zero. Because the frontal cortex contains more than two-thirds of the corpus callosum, the frontal vertex can be considered the site of time zero if the bilateral synchronization originates from the primary epileptogenic zone and spreads rapidly via the transcallosal pathway [2,4,9]. We also defined the event period from −0.5 s to +0.5 s as time zero based on the electrode in the frontal vertex. Known channel location was applied to the locations of the recording electrodes (EEGLAB software toolbox for Matlab, The math works, Inc. v 11.0). Next, we extracted events automatically throughout the EEG recordings using the EEGLAB software toolbox. We selected GSW visually among the automatically detected GSW and the excluded GSW that was mixed with artifacts. The number of GSW was 162.42 ± 65.79 (mean ± standard deviation) in group A and 76.67 ± 38.8 in group B.

GSW should consist of independent signals from certain areas. If these signals are observed, the primary epileptogenic zones could be identified from these source signals of the GSW, especially at the onset of the spike. Therefore, the GSW during an event were decomposed into the maximal temporally independent components available using independent component analysis instead of a distributed source model. To perform electrical source imaging of the independent components, the DIPFIT software plug-in (EEGLAB software toolbox for Matlab, The math works, Inc. v 11.0) was used with a standardized boundary element model from the Montreal Neurological Institute coordinates. Nineteen sources were decomposed by independent component analysis and each electrical source was selected only if its residual variance was below 30%. To identify the primary epileptogenic zone, dDTF-based MVAR was applied to each independent signal of the GSW. A time window of 500 ms was selected with stepwise advances of 100 ms; these parameters were based on the amount of data that would be sufficient and the lowest frequency of interest. Simulations based on the dDTF results were obtained and interpreted using the time frequency grid with brain movie three dimensions in the Source Information Flow Toolbox [12].

Table 1
Clinical characteristics of LGS patients who underwent surgical treatment.

	Group A ($n = 12$)	Group B ($n = 15$)
Age[a] (yrs)	9.6 (5.0–22.0)	11.0 (5.8–18.5)
Sex (M:F)	6:6	11:4
Seizure onset[a] (yrs)	1.0 (0.3–4.0)	0.9 (0.3–7.8)
Age at surgery[a] (yrs)	5.6 (3.4–17.4)	8.1 (3.1–15.1)
Number of AEDs before surgery[a] (yrs)	4 (3–5)	4 (4–5)
F/U duration after last surgery[a] (yrs)	3.6 (0.6–5.6)	3.3 (2.2–6.1)
Normal MRI findings, cases (%)	5 (41.7)	5 (33.3)
Focal evidence of EEG (%)	12 (100.0)	0
MRI	7 (58.3)	0
PET	6 (50.0)	0
SPECT	6 (50.0)	0
Surgical treatment	Resection	Corpus callosotomy
Surgical outcome, cases (%)		
Good (Engel Class I or II)	12 (100.0)	3 (20.0)
Poor (Engel Class III or IV)	0	12 (80.0)

AED, antiepileptic drug; F/U, follow-up.
[a] The data are presented as medians (ranges).

2.3. Localization of the primary epileptogenic zone identified by dDTF analysis

The dDTF algorithm was first introduced by Korzeniewska et al. [13] to overcome the limitations of directed transfer function (DTF), particularly the generation of incorrect pathways, and to improve the distinction between direct and indirect causality. dDTF analysis has been shown to be a compact method with low false causality and high spectral selectivity. dDTF analysis has also been shown to be a suitable method that tolerates noise constants or phase disturbances and is insensitive to volume conduction [14,15]. Because volume conduction has an influence on the amplitudes of the electric field on the scalp, dDTF is based on phase differences between the signals.

The DTF method is based on an MVAR model fitted to the source activities of the GSW. In the MVAR model, a multi-source process represents vector X of n source activities of GSW, as long as $X(t) = (X_1(t), X_2(t), \ldots, X_n(t))^T$, where $X(t)$ denotes the data vector in time and t denotes time. Thus, the MVAR equation can be written as follows:

$$X(t) = \sum_{k=1}^{p} A(k)X(t-k) + E(t)$$

where $E(t)$ denotes the vector of the white noise process in time t, $A(k)$ is an $N \times N$ matrix of model coefficients, and p is the model order. In our study, the appropriate model order was selected according to the Schwarz–Bayesian criterion for the MVAR process to prevent the over-fitting of a consistent estimator [16]. The validity of the model order was confirmed based on the stability of the MVAR process and the portmanteau statistical test, which determines the whiteness of the residuals and indicates a good model when insignificant.

The DTF is defined as the value of the transfer matrix H_{ij} that corresponds to the ratio of the inflow from signal j to signal i at a specific frequency. This ratio ranges from 0 to 1. A value close to 1 indicates that signal j causes most of signal i, whereas a ratio of 0 indicates that there is no flow from signal j to signal i at this frequency.

$$\mathrm{DTF}_{ij}(f) = \frac{H_{ij}(f)}{\sqrt{\sum_{k=1}^{m} |H_{ik}(f)|^2}}$$

DTF suggests the directionality between signals but does not identify whether the pathways are direct or indirect. dDTF, a modified DTF method, is unaffected by the frequency because it uses all frequencies rather than one specific frequency. Furthermore, it can also distinguish between the direct and indirect relationships between the signals in addition to specifying directionality. Thus, dDTF consists of the DTF of all frequencies and the partial coherence, and it is calculated as follows:

$$\mathrm{dDTF}_{ij}(f) = \mathrm{pCoh}_{ij}(f) \cdot \mathrm{ffDTF}_{ij}(f)$$

where ffDTF is defined using the following equation for the full – frequency (ff):

$$\mathrm{ffDTF}_{ij}(f) = \frac{H_{ij}(f)}{\sqrt{\sum_{f=f1}^{fN_f} \sum_{k=1}^{m} |H_{ik}(f)|^2}}$$

and partial coherence (pCoh) is defined using the following equation containing $M_{ij}(f)$, which indicates the minor obtained by eliminating the i and j components from the spectral matrix:

$$\mathrm{pCoh}_{ij}(f) = \frac{M_{ij}(f)}{\sqrt{M_{ii}(f)M_{jj}(f)}}$$

After the dDTF values were obtained using the above equations, the cortical areas identified via the dDTF analysis were compared with the resected areas in group A and with the postoperative EEGs from group B. The concordance of the areas identified via dDTF analysis with the resected areas in group A and with the areas containing epileptogenic discharges based on the postoperative EEGs from group B was evaluated as either hemispheric lateralization or lobar localization.

2.4. Statistical significance of causality

To determine causality, we applied surrogate data to a nonparametric statistical significance test. Surrogate data were utilized to compare the values between signals and to estimate the expected probability of the dDTF values under the null hypothesis of no causality. We permuted the shuffling and causality process 250 times for each source in the time series to calculate a reasonable estimate. We set the adjusted significance value at $p < 0.05$ and used the false discovery rate as a correction for multiple comparisons [17]. The Chi-square test, Fisher's exact test and the Mann–Whitney U test were used to determine the differences between group A and group B, and p values <0.05 were considered significant.

3. Results

The primary epileptogenic zone identified by the dDTF analysis included the resected areas for all of the patients and was lateralized or localized in 10 patients in group A during the awake and asleep states (Table 2). In a 12-year-old female patient in group A who underwent left hemispherotomy and exhibited Engel Class I, the directional causality of brain connectivity for the GSW during the awake state was localized in the left superior frontal gyrus and the left middle frontal gyrus (Fig. 1), while it was localized in the left basal ganglia during the sleep state. In contrast, the primary epileptogenic zone identified by the dDTF analysis revealed predominant bilateral or multifocal areas in 14 patients in group B during the awake and asleep states; however, they did not match the areas of the interictal spike with disrupted GSW on the postoperative EEG (Table 3). Despite this possibility, we determined whether the epileptogenic origin was unifocal or multifocal in both groups by analyzing the GSW. Therefore, the dDTF results exhibited concordance for laterality (83.3%) in group A and bilaterality (93.3%) in group B (Table 4) ($p < 0.01$). The number of primary epileptogenic zones according to the dDTF analysis was identified as one area in four, two areas in three and three areas in five patients from group A, and it was more than three areas in 10 patients from group B ($p < 0.05$). 91.7% of group A and 100% of group B showed the frontal area as the primary epileptogenic zones identified by dDTF analysis, and 36.1% of group A and 24.5%

Table 2
Primary epileptogenic zone identified via dDTF analysis in group A during the awake and sleep states.

Sex/age	MRI findings	Areas based on dDTF analysis during the awake state	Areas based on dDTF analysis during the sleep state	Resected areas	Pathology
M/9	Normal	Rt. P, O	Rt. F, T	Rt. T, P, O	FCD Ib
M/9	Rt. F CD	Rt. F	Rt. F, O	Rt. F, T, O	FCD Ia
F/12	Lt. CD	Lt. F	Lt. BG	Lt. H	Polymicrogyria
M/19	Normal	Rt. T, O	Rt. F	Rt. T, O	FCD IIa
F/16	Rt. F CD	Rt. F	Rt. F, T	Rt. F, T	FCD IIa
F/8	Lt. O cerebromalacia	Lt. O	Lt. O	Lt. T, O	Gliosis
F/22	Normal	Rt. F	Rt. F	Rt. F,	FCD IIa
M/10	Lt. P CD	Lt. F, T, Rt. F	Lt. F, O	Lt. P, T, O	FCD Ia
M/8	Rt. F CD	Rt. F, T	Rt. T, Lt. F	Rt. F, T	FCD IIa
F/19	Lt. F CM	Lt. F	Lt. F	Lt. F	FCD IIa
F/5	Normal	Lt. F	Lt. F	Lt. F, T	Gliosis
M/6	Normal	Rt. F, O	Rt. T	Rt. F, T	NPD

dDTF, direct directed transfer function; CD, cortical dysplasia; CM, cavernous malformation; FCD, focal cortical dysplasia; Rt., right; Lt., left; F, frontal; P, parietal; T, temporal; O, occipital; BG, basal ganglia; NPD, no pathological diagnosis.

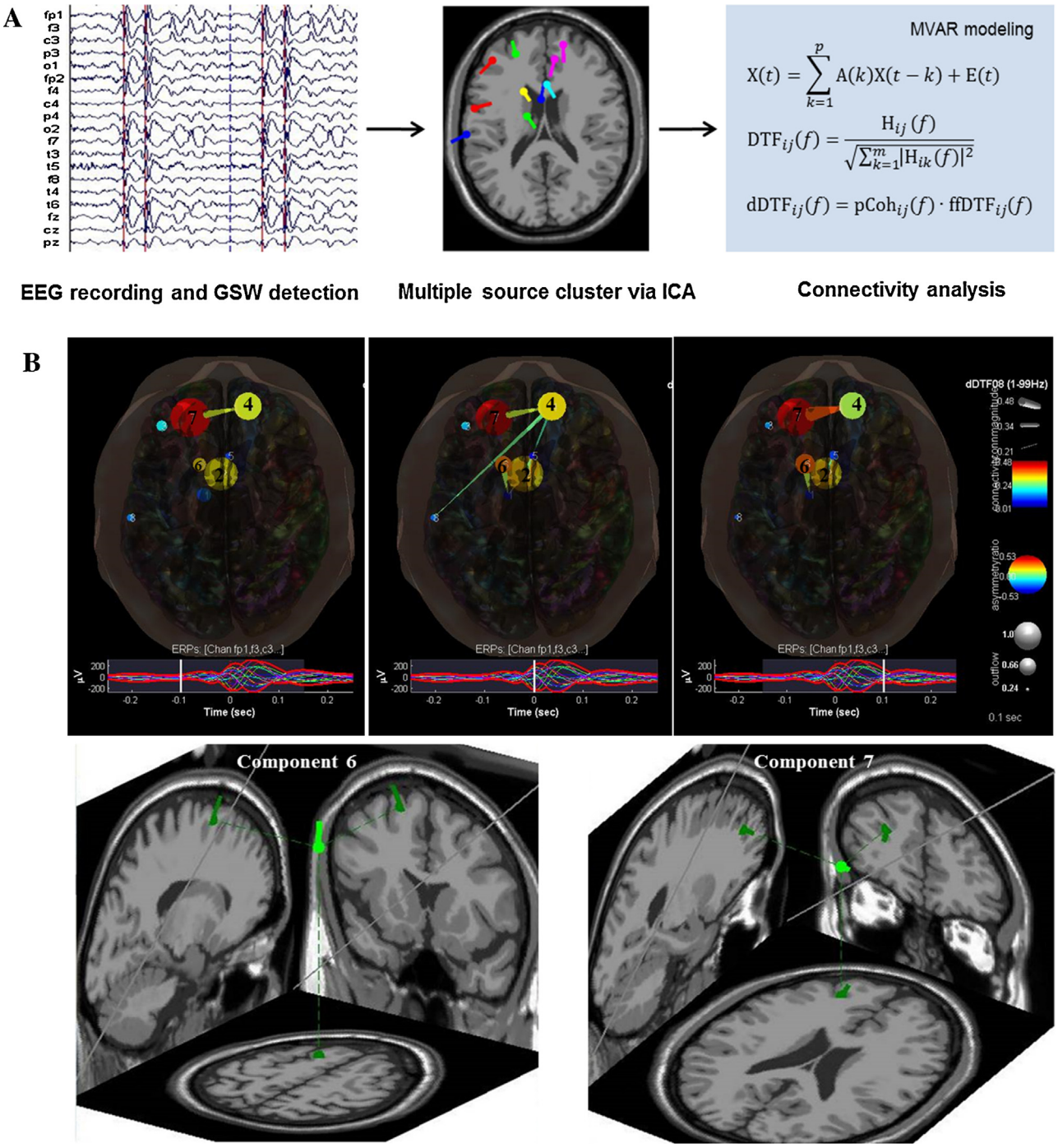

Fig. 1. Directional causality of brain connectivity during the awake state in a 12-year-old female patient in group A who underwent left hemispherotomy and exhibited Engel Class I. (A) Schematic diagram of the process used in our study. (B) Three-dimensional simulation of the directional causality for each source activity according to a time series (−0.1, 0, 0.1 s). The activity of component 6 was increased, and the activity of component 7 was transferred to component 4 (yellow circle, Rt. frontal area), which was then transferred to component 2 (yellow circle, frontal vertex) during the time series. Components 6 and 7 were predicted to represent the primary epileptogenic zone that initiated the GSW. The MRI shows component 6, which was localized to the left superior frontal gyrus and component 7, which was localized to the left middle frontal gyrus. Brain connectivity is statistically significant at $p < 0.05$. GSW, generalized sharp and wave discharges; ICA, independent component analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of group B showed extra-frontal areas; however, these calculations did not include the deep gray matter and the corpus callosum ($p > 0.05$). In the cases of localization to extra-frontal areas, the primary epileptogenic zone identified by the dDTF analysis was concordant in terms of lateralization of the epileptogenic lesion in all of the patients in group A (Table 5). Surprisingly, only one patient with left hemisphere cortical dysplasia in group A exhibited localization to the deep gray matter, whereas 10 patients in group B exhibited localization to the deep gray matter or the corpus callosum; one patient showed localization to both the deep gray matter and the corpus callosum.

4. Discussion

dDTF-based MVAR provides evidence for directional causality and reflects complex epileptic neuronal networks. Currently, few

Table 3
Primary epileptogenic zone identified via dDTF analysis in group B during the awake and sleep states.

Sex/age	MRI findings	Areas based on dDTF analysis during the awake state	Areas based on dDTF analysis during the sleep state	EEG results after CC	Surgical outcome
M/14	Polymicrogyria	Rt. F, Lt. P	Lt. O, PV	Both C, Lt. F	IV
M/15	Normal	Rt. F, O	Lt. F	Both F	III
M/12	Diffuse CD	Rt. F, BG	Lt. F, Rt. CC	Both F	IV
M/9	Pachygyria	Lt. F, Rt. O	Lt. F, O, CC Rt. O	Both F, Rt. C	IV
F/6	Mild atrophy	Lt. T, O, Rt. F	Lt. P, O, Rt. F, thal.	Both F, T, O	IV
M/8	Ventriculomegaly	Lt. T, Rt. F, CC	Lt. F	Both F, O	III
M/6	Normal	Rt. F, Rt. BG	Rt. F,	Both F, O, Lt. T	IV
M/12	Mild atrophy	Rt. F, CC	Lt. F, Rt. F	Both F, Rt. O, Rt. T	II
M/9	Cerebromalacia	Lt. F, T	FV	Both H	IV
M/14	Cerebellar atrophy	Rt. F, FV	Lt. F	Both F	IV
M/11	Mild atrophy	Lt. F, Lt. BG Rt. P	Lt. F, P, T	Lt. H, Rt. P	I
F/10	Normal	Lt. F, Rt. F	Lt. F, Rt. F	Both F	III
F/10	Normal	Both thalami	FV	Both H	IV
M/13	Band heterotopias	Lt. F, Rt. F, Rt. BG	Rt. F, Lt. T	Both F, T	II
F/18	Normal	Rt. F, Lt. F	Lt. BG	Both F	IV

dDTF, direct directed transfer function; Rt., right; Lt., left; F, frontal; P, parietal; T, temporal; O, occipital; PV, parietal vertex; FV, frontal vertex; H, hemisphere; BG, basal ganglia; CC, corpus callosum.

Table 4
Concordance of the cortical epileptogenic zones identified via dDTF analysis with the resection site in group A and with the postoperative EEG results after corpus callosotomy in group B.

dDTF results for generalized sharp and wave discharges	Concordant cases (%)
Primary epileptogenic zone based on dDTF analysis in group A (N = 12)	
Within resected areas only	7 (58.3)
Within resected areas + independent ipsilateral independent area	3 (25.0)
Within resected areas + independent contralateral independent area	2 (16.7)
Primary epileptogenic zone based on dDTF analysis in group B (N = 15)	
Unilateral or localized area	1 (6.7)
Bilateral or multifocal area	14 (93.3)

dDTF, direct directed transfer function.

studies have investigated whether dDTF-based MVAR is a superior method for analyzing other EEG datasets, such as event-related electrical stimuli, or for detecting the sources of the generation and propagation of epileptic discharges in a limited number of available epilepsy cases [7,15,18–20]. We were not able to find a meaningful concordance between dDTF findings and the resective areas from analyzing each awake and asleep state, separately. However, we found that the resective surgery group usually displayed a unilateral primary epileptogenic zone that corresponded with the resected areas when we considered dDTF results during both awake and asleep state. Each resected area was confirmed as focal cortical dysplasia, except four cases, which included polymicrogyria in one, normal in one and gliosis in two cases on the pathological findings. The corpus callosotomy group displayed multifocal or bilateral epileptogenic zones. The application of dDTF-based MVAR helps in determining in which group a patient belongs.

The source activities of GSW that displayed bilateral synchronization are typically localized to the frontal area, regardless of whether the frontal area is responsible for the primary or secondary GSW [5,8,9]. We found that frontal areas were the dominant areas in Lennox–Gastaut syndrome, and the dDTF results were localized to the frontal area in 91.7% and 100% of the patients in groups A and B, respectively. In group A, some discordant results between the primary epileptogenic zone identified by the dDTF analysis and the resected areas appeared to be primarily due to the localization in the frontal areas. These results indicate that frontal areas contributed to the generation of GSW from the epileptogenic zone via thalamocortical circuits. One study that reported the difference between the primary and secondary GSW detected the dipole sources via the localization of the largest potential contributor to the GSW without directional causality [5]. However, the dipole source displaying the strongest activity may not represent the primary epileptogenic zone because the dipole source of a minor potential contributor to the GSW may represent

Table 5
Localized areas based on dDTF analysis in groups A and B.

Location	Group A			Group B
	No. of cases (%)	Concordance of lateralization (%)	Concordance of localization (%)	No. of cases (%)
Cortex	12			15
Frontal	11 (91.7)	9 (81.8)	8 (72.7)	15 (100)
Temporal	6 (50.0)	6 (100)	6 (100)	4 (26.7)
Parietal	1 (8.3)	1 (100)	1 (100)	3 (20.0)
Occipital	6 (50.0)	6 (100)	5 (83.3)	4 (26.7)
Deep gray matter	1			7
Basal ganglia	1 (8.3)			5 (33.3)
Thalamus				2 (13.3)
Corpus callosum				4 (26.7)

dDTF, direct directed transfer function.

the primary epileptogenic zone, which would then stimulate other sources, even if it is not the strongest potential contributor. We detected the primary epileptogenic zone via directional causality and found its superiority, which showed highly concordant results in group A. The concordance of the extra-frontal areas in particular seemed to be superior to the frontal area. Additionally, we found that group A exhibited no localization in the deep gray matter, whereas group B did, even though functional MRI analysis has revealed the activation of deep gray matter in LGS [21]. Specifically, the activation of deep gray matter as the primary epileptogenic zone could be associated with the generalization of GSW and may be an argument against the use of resective surgery; however, we have a limitation in using subcortical sources, as well as cortical sources, to compare the different findings between groups A and B because subcortical sources exhibited the possibility of a summation of cortical signals. Still, using dDTF analysis, we detected deeper neuronal networks, such as the primary epileptogenic zone, that stimulated other areas, which were confirmed based on histopathological results following surgical resection.

DTF is an appropriate tool for analyzing brain connectivity. However, DTF provides weak evidence for supporting the directional causality for direct and indirect relationships. dDTF is an improvement in that it applies the partial coherence function without a specific frequency to identify direct relationships, and it displays a lower false causality than DTF using EEG data [13–15,22]. It is uncertain that the primary epileptogenic zone found by directional causality is the actual epileptogenic focus. However, the concordance of the dDTF results with the resected surgical areas observed in our study supports this idea. A previous study on ictal onset using intracranial EEG in LGS reported that the use of DTF was superior for identifying the primary epileptogenic zone and that the results corresponded well with the resected areas [23]. Wilke et al. [24] also reported that the epileptogenic foci corresponded well with the sources identified by DTF analysis for interictal spikes based on electrocorticography in focal epilepsy. Furthermore, in focal cortical dysplasia, the source localization of interictal spikes based on a scalp EEG was associated with the epileptogenic zone over the visible areas based on MRI, and this analysis showed both the epileptogenic zone and remote areas, which suggests network organization [25]. Thus, the source of interictal spikes could also be multiple independent epileptogenic foci or a single epileptogenic focus that spreads to other remote areas. In our study, the analysis of interictal GSW using dDTF facilitated the identification of the primary epileptogenic zone in LGS patients. We found that there are either multiple independent epileptogenic foci or a single epileptogenic focus that spreads to other remote areas [24,25]. Primary epileptogenic zones could be hidden in GSW data in LGS, but they can be detected using source analyses, such as an analysis of directional causality.

An EEG displays high temporal resolution but limited spatial resolution. Although we used dDTF-based MVAR to improve the spatial identification of the primary epileptogenic zone, our data still displayed limited spatial resolution. This limitation occurred because we used the 10–20 international system and MRI template rather than individual MRI data for electrical source imaging. To provide more accurate spatial resolution, dense array EEG, which consists of more than 100 channels, can be used. The source estimation of the interictal spikes based on dense array EEG using 256 channels produced similar results with regard to the areas of seizure onset and the interictal spike activity based on intracranial EEG. This method could reduce the need for invasive intracranial EEG in neocortical epilepsy patients [26]. If dense array EEG with individual MRI for electric source imaging was applied, we would obtain more precise spatial and temporal resolution for directional causality, and we would avoid invasive intracranial monitoring. Further investigation of directional causality using dense array EEG in LGS is needed to better understand the epileptic neuronal network.

In conclusion, the dDTF analysis of GSW in resective surgical patients revealed concordance of the primary epileptogenic zone. This analysis provides valuable information identifying LGS patients who are good resective surgery candidates. Further research of dDTF analysis is required to determine the underlying pathogenesis of the epileptogenic zone that induces the generation of secondary generalized epileptic encephalopathy.

Conflict of interest statement

The authors report no conflicts of interest.

Acknowledgments

This work was supported by the National Research Foundation of Korea grant funded by the Korean Government (2012R1A2A2A01012608).

References

[1] Kobayashi K, Ohtsuka Y, Oka E, Ohtahara S. Primary and secondary bilateral synchrony in epilepsy: differentiation by estimation of interhemispheric small time differences during short spike-wave activity. Electroencephalogr Clin Neurophysiol 1992;83:93–103.
[2] Hur YJ, Kang HC, Kim DS, Choi SR, Kim HD, Lee JS. Uncovered primary seizure foci in Lennox–Gastaut syndrome after corpus callosotomy. Brain Dev 2011;33:672–7.
[3] Lee YJ, Kang HC, Lee JS, Kim SH, Kim DS, Shim KW, et al. Resective pediatric epilepsy surgery in Lennox–Gastaut syndrome. Pediatrics 2010;125:58–66.
[4] Sitnikova E, Dikanev T, Smirnov D, Bezruchko B, van Luijtelaar G. Granger causality: cortico-thalamic interdependencies during absence seizures in WAG/Rij rats. J Neurosci Methods 2008;170:245–54.
[5] Jung KY, Kim JM, Kim DW, Chung CS. Independent component analysis of generalized spike-and-wave discharges: primary versus secondary bilateral synchrony. Clin Neurophysiol 2005;116:913–9.
[6] Ding L, Worrell GA, Lagerlund TD, He B. Ictal source analysis: localization and imaging of causal interactions in humans. Neuroimage 2007;34:575–86.
[7] Lin FH, Hara K, Solo V, Vangel M, Belliveau JW, Stufflebeam SM, et al. Dynamic Granger–Geweke causality modeling with application to interictal spike propagation. Hum Brain Mapp 2009;30:1877–86.
[8] Santiago-Rodríguez E, Harmony T, Fernández-Bouzas A, Hernández-Balderas A, Martínez-López M, Graef A, et al. Source analysis of polyspike and wave complexes in juvenile myoclonic epilepsy. Seizure 2002;11:320–4.
[9] Holmes MD, Brown M, Tucker DM. Are "generalized" seizures truly generalized? Evidence of localized mesial frontal and frontopolar discharges in absence. Epilepsia 2004;45:1568–79.
[10] Engel Jr J, Van Ness P, Rasmussen T, Ojemann L. Outcome with respect to epileptic seizure. In: Engel J, editor. Surgical treatment of the epilepsies. 2nd ed., New York: Raven; 1993. p. 609–21.
[11] Aronica E, Becker AJ, Sperafico R. Malformations of cortical development. Brain Pathol 2012;22:380–401.
[12] He Y, Evans A. Graph theoretical modeling of brain connectivity. Curr Opin Neurol 2010;23:341–50.
[13] Korzeniewska A, Mańczak M, Kamiński M, Blinowska KJ, Kasicki S. Determination of information flow direction among brain structures by a modified directed transfer function (dDTF) method. J Neurosci Methods 2003;125:195–207.
[14] Kuś R, Kamiński M, Blinowska KJ. Determination of EEG activity propagation: pair-wise versus multichannel estimate. IEEE Trans Biomed Eng 2004;51:1501–10.
[15] Fasoula A, Attal Y, Schwartz D. Comparative performance evaluation of data-driven causality measures applied to brain networks. J Neurosci Methods 2013;215:170–89.
[16] Schwarz G. Estimating the dimension of model. Ann Stat 1978;6:461–4.
[17] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 1995;57:289–300.
[18] Schlögl A, Supp G. Analyzing event-related EEG data with multivariate autoregressive parameters. Prog Brain Res 2006;159:135–47.
[19] Astolfi L, Cincotti F, Mattia D, Marciani MG, Baccala LA, de Vico Fallani F, et al. Comparison of different cortical connectivity estimators for high-resolution EEG recordings. Hum Brain Mapp 2007;28:143–57.
[20] Florin E, Gross J, Pfeifer J, Fink GR, Timmermann L. Reliability of multivariate causality measures for neural data. J Neurosci Methods 2011;198:344–58.

[21] Siniatchkin M, Coropceanu D, Moller F, Boor R, Stephani U. EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox–Gastaut syndrome. Epilepsia 2011;52:766–74.
[22] Korzeniewska A, Crainiceanu CM, Kus R, Franaszczuk PJ, Crone NE. Dynamics of event-related causality in brain electrical activity. Hum Brain Mapp 2008;29:1170–92.
[23] Jung YJ, Kang HC, Choi KO, Lee JS, Kim DS, Cho JH, et al. Localization of ictal onset zones in Lennox–Gastaut syndrome using directional connectivity analysis of intracranial electroencephalography. Seizure 2011;20:449–57.
[24] Wilke C, van Drongelen W, Kohrman M, He B. Identification of epileptogenic foci from causal analysis of ECoG interictal spike activity. Clin Neurophysiol 2009;120:1449–56.
[25] Blenkmann A, Seifer G, Princich JP, Consalvo D, Kochen S, Muravchik C. Association between equivalent current dipole source localization and focal cortical dysplasia in epilepsy patients. Epilepsy Res 2012;98:223–31.
[26] Yamazaki M, Tucker DM, Terrill M, Fujimoto A, Yamamoto T. Dense array EEG source estimation in neocortical epilepsy. Front Neurol 2013;4:42.