The role of the direct directed transfer function in identifying the primary epileptogenic zone from generalized sharp and wave discharges in Lennox-Gastaut syndrome

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Directed by Professor Heung Dong Kim

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<TABLE OF CONTENTS>

ABSTRACT ····· 1
I. INTRODUCTION ····· 3
II. MATERIALS AND METHODS ····· 5
1. Patients ····· 5
2. Data acquisition and source localization ····· 6
3. Localization of the primary epileptogenic zone via dDTF ····· 7
4. Statistical significance of causality ····· 10
III. RESULTS ····· 11
1. Clinical characteristics of patients ····· 11
2. Source localization for generalized sharp and wave discharge ····· 11
3. dDTF results comparing to resective areas or postoperative EEG · 12
IV. DISCUSSION ····· 19
V. CONCLUSION ····· 22

REFERENCES ····· 23
ABSTRACT (IN KOREAN) ····· 27

LIST OF FIGURES

Figure 1. The cluster of components by independent component analysis (ICA) ·····12

Figure 2. Directional causality of brain connectivity for generalized sharp and wave discharges during the awake state in a 12-year-old female patient who underwent left hemispherotomy with Engel class I (Group A) ·····15

Figure 3. Directional causality of brain connectivity for generalized sharp and wave discharges during the asleep state in a 12-year-old female patient who underwent left hemispherotomy with Engel class I (Group A) ·····16

LIST OF TABLES

Table 1. Clinical characteristics of patients with Lennox-Gastaut syndrome who underwent corpus callosotomy ·····11

Table 2. Primary epileptogenic zone identified by dDTF in Group A during the awake and the asleep states……13

Table 3. Primary epileptogenic zone identified by dDTF in Group B during awake and asleep states……14

Table 4. The number of localizations by dDTF in Lennox-Gastaut syndrome……17

Table 5. The concordance rate of the cortical epileptogenic zone identified by dDTF when compared with the resection site in Group A and with postoperative EEG after corpus callosotomy in Group B ……18

Table 6. The location by dDTF in group A……18

Table 7. The location by dDTF in group B……19

Table 8. Diagnostic sensitivity, specificty and positive predictive value of dDTF for lateralization and localization in Lennox-Gastaut syndrome……19

<ABSTRACT>

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Purpose: In intractable epilepsy, the patient can be freed of seizures by removing the epileptogenic zone. However, identifying the primary epileptogenic zone is particularly difficult in Lennox-Gastaut syndrome (LGS), despite current multimodal approaches. I identified the primary epileptogenic zone via brain connectivity of the generalized sharp and wave discharge (GSW). I also reviewed the differences between LGS patients who had the epileptogenic zones removed and those who did not.

Methods: I reviewed LGS patients who underwent surgical treatment from 2005 to 2013. I separated them into a group (Group A) who underwent resective surgery for epileptogenic zones (N=12) with good surgical outcome, and a group (Group B) who only underwent corpus callostomy and retained independent bilateral epileptogenesity (N=15). I analyzed the GSW in preoperative electroencephalography to identify the primary epileptogenic areas by using direct directed transfer function (dDTF)- based a multivariate autoregressive model. I compared the areas identified by direct directed transfer

function with the resection areas in Group A and with the postoperative EEG in Group B.

Results: The results of dDTF showed localization or lateralization in 83.3% of Group A, and while bilateral or multifocal localization in 93.3% of Group B (p<0.01). The localization shown by dDTF included resective areas in all patients and agreed with resective areas in 58.3% of Group A. Among areas identified by dDTF, frontal area was localized at 91.7% and 100%, while extra-frontal areas were localized at mean 33.3% and 24.5% in group A and group B, respectively. The diagnostic sensitivity of dDTF for lateralization and localization was 83.3% and 62.5%, respectively, and the specificity was 86.7% and 63.2%, respectively.

Conclusion: Analyzing the GSW by using the dDTF might be a valuable approach for the identification of the primary epileptic zone in LGS, alongside a multimodal approach.

Key words: direct directed transfer function, Lennox-Gastaut syndrome, generalized sharp and wave discharges

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I. INTRODUCTION

Lennox-Gastaut syndrome (LGS) is characterized by multiple types of seizure, electroencephalographic (EEG) features such as generalized slow sharp and wave discharges and generalized paroxysmal fast activities, and mental retardation. Generalized sharp and wave discharges (GSW), presenting with bilateral synchronization in secondary generalized epileptic encephalopathy such as LGS, can originate from the primary epileptogenic zone via transcallosal pathway and can be revealed by rapid spread via a centrencephalic circuit [1-3]. Sometimes, the primary epileptogenic zone can be identified using a multimodal approach. Resective surgery for epileptogenic zone showed a seizure-free surgical outcome rate of 59.2 % in LGS[4,5]. Identification of the primary epileptogenic zone is the main prerequisite for surgical treatment, but it is difficult in LGS. GSW, especially, often fails to reveal the primary epileptogenic zone if it is not accompanied by the types of the focal EEG features which have been described in previous studies[4,5]. Sometimes, hemispheric asymmetry in EEG and other modalities after corpus callosotomy

can be used to identify pre-existing primary epileptogenic zone and to enable resective surgery[4,6].

Substantively, the consistency between the real epileptic foci and the primary epileptogenic zone as recorded by EEG is not confirmative. The concept of inverse problem for source analysis has come to be magnified as a solution for this problem. Actually, many models for source analysis including the equivalent dipole model, independent component analysis (ICA) and various methods for brain connectivity have been used to identify source localization of GSW as well as focal spikes[2,3,7-10]. Usually source analysis using dipole modeling for GSW reveals a cluster of sources in medial or lateral frontal, frontal polar and orbito-frontal areas[3,9,10]. However, GSW is composed of an intricate sum of all source activities, normal brain activities and noise. Therefore, the separation of source activities from others should be obtained by methods such as ICA. ICA can separate statistically independent components from intricate signals without separation for the same spatial topography, and it can be also used to identify the localization and propagation of spikes[3,11,12]. Multiple components extracted by ICA can be considered either to be a single epileptic source that might generate other components or to be multiple independent epileptic sources[11]. In other words, ICA cannot suggest the directionality and causality between mutual information for multiple components which contributes to GSW.

To overcome these drawbacks, Granger causality combined with brain connectivity using multivariate autoregressive (MVAR) model has been recently introduced as a stochastic qualifier. Granger causality reveals that X(n) may cause Y(n) without Y(n) causing X(n) if two different signals exist and there is relationship between the time series. That is, Granger causality can identify the causality between different cortical areas that have direct or indirect relationships to electrical signals in the development of epileptic discharges[2,8]. Kus et al.[13] studied the differences between pair-wise and multichannel

estimates and reported the superiority of MVAR for the localization of sources from electrical signals. Granger causality using direct directed transfer function (dDTF) or partial directed coherence has been applied to the generation and propagation of the epileptic discharges and has been interpreted as directionality for brain connectivity[13-15]. Partial directed coherence and dDTF- based MVAR have been proven to be the most interesting methods for characterizing causal directionality between different brain signals in event- related EEG data[14]. These methods have also been used in a previous study of the epileptic activity of interictal spikes propagating from the right frontal area to the left frontal area[8]. However, the application and validation of dDTF- based MVAR is not straightforward and is mainly limited to modeling electrical discharges in animal. The dDTF- based MVAR model is rarely applied in studies in human. Therefore, I analyzed GSW without localization in LGS through dDTF- based MVAR to identify the pre-existing primary epileptogenic zone. I also validated these methods for direct causality, which can be worth noting with regard to the generation and propagation of secondary bilateral synchronization among different brain areas.

II. MATERIALS AND METHODS

1. Patients

Fifty-five patients who had undergone surgical treatment for intractable LGS from November 2005 to July 2013 were enrolled. Patients who had undergone prior brain surgery or other procedures before surgical treatment were excluded because of the possibility of electrical or spatial distortions for computational analysis. Patients with partial or incomplete corpus callosotomy, despite having a plan for complete resection as palliative surgery were also excluded because of the possibility of propagation and generation of epileptic discharges via the

remainder of the corpus callosum. The extent of callosotomy was confirmed by a postoperative magnetic resonance imaging (MRI). Twelve patients who had primary epileptogenic zones confirmed by resective surgery and showed good surgical outcome with Engel class I, were included in Group A. Fifteen patients who had independent bilateral or multifocal epileptogenic foci after corpus callosotomy were included in Group B. All patients underwent presurgical evaluation including clinical characteristics, video EEG monitoring, MRI and functional modalities, such as single photon emission computed tomography or positron emission tomography, to enable considerable agreement with regard to the primary epileptogenic zone. Resective surgery was performed based upon the identified primary epileptogenic zone using multimodal approach, and surgical outcomes were determined using Engel's classification at a later visit to an outpatient clinic, with a median follow-up duration of 3.6 years[16]. The primary epileptogenic zone was confirmed by the histopathological findings, which were reviewed by an experienced neuropathologist. The histopathological findings were classified into different subtype of focal cortical malformation according to the International League Against Epilepsy classification system[17]. All patients underwent postoperative EEG between 3 and 6 months after surgical treatment. I analyzed GSW of the EEG before surgery in two groups to identify the primary epileptogenic zone via dDTF-based MVAR, and I studied the difference about the epileptic network of GSW between the two groups.

2. Data acquisition and source localization

Video EEG monitoring before surgery using a digital EEG acquisition system (Grass Telefactor, Astro-Med Inc., West Warwick, RI, USA) was completed over 48 hours with 22 electrodes placed on the scalp in accordance with the international 10-20 system and recorded at a sampling rate of 200 Hz and band

pass width from 0.5 Hz to 70 Hz. EEG recording was interpreted by epileptologist to identify characteristic EEG features for LGS.

I obtained recordings for 10 minutes each during both sleep and wake states from video EEG monitoring. I selected GSW without lateralization or localization for 10 minutes semi-automatically and marked each event with its peak at the electrode of the frontal vertex, which was timed at zero second. Because the frontal cortex occupies over two third of corpus callosum, it can be used as the peak point if bilateral synchronization is originated from the primary epileptogenic zone and spreads rapidly via the transcallosal pathway[2,4,10]. I defined the event time from - 0.5 seconds to + 0.5 seconds, centered at the peak time with the electrode of the frontal vertex representing zero second. Event-related potentials were separated with an ICA tool and revealed the components of largest potential contribution for GSW during event duration. The equivalent dipole sources for the independent components were localized using a DIPFIT plug-in: equivalent dipole source localization of independent components (EEGLAB v 11.0). dDTF- based MVAR was applied to identify the primary epileptogenic zone by using the Source Information flow Toolbox plug-in. Ensemble normalization was used as preprocessing step of MVAR to remove the event-related potentials, because ongoing oscillations revealed more than a considerable neuronal network for event-related potentials. Window length was selected as 500 milliseconds (ms), with stepwise advances of 100 ms based upon consideration of 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 3D in Source Information Flow Toolbox.

3. Localization of the primary epileptogenic zone via dDTF

The source activities of GSW were applied using dDTF with MVAVR to

identify the primary epileptogenic zone. The dDTF algorithm was first introduced by Korzeniewska et al. [18] to overcome the limitations of DTF, namely, in the generation of incorrect pathways, and to distinguish better direct and indirect causality. dDTF has been shown demonstrated to be a compact method with low false causality and high spectral selectivity. dDTF has also been demonstrated to be a suitable method to tolerate noise constants or phase disturbances and to be insensitive to volume conduction[13,19].

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

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

where E(t) denotes the vector of the white noise process in time t, A(k) is an N x N matrix of model coefficients, and p is the model order. In my study, the proper model order was selected by using the Schwarz-Bayesian Criterion for the MVAR process to prevent over-fitting of consistent estimator[20]. The validity of the model order was tested by the stability of the MVAR process and the portmanteau statistic test, which determines the whiteness of the residuals and indicates a good model when insignificant. The MVAR model is then transformed into the frequency domain for spectral analysis as an equation involving the transfer matrix of the system, H(f), and a specific frequency, f, as follows:

$$X(f) = A^{-1}(f)E(f) = H(f)E(f)$$

that is,

$$H(f) = A^{-1}(f)$$

where A(f) is described by Δt, the temporal interval between two signals

$$A(f) = \sum_{k=0}^{p} A(k)\, e^{-2j\pi k \Delta t}$$

The DTF is defined by the ratio using the transfer matrix H_{ij} corresponding to the inflow from signal *j* to signal *i* at a specific frequency. The ratio ranges from 0 to 1. If its value is close to 1, this indicates that signal *j* causes most of signal *i* while a ratio of 0 indicates no flow from signal *j* to signal *i* at this frequency.

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

The DTF suggests directionality between signals but does not identify direct or indirect pathways. dDTF as a modified method for determining DTF is unaffected by the frequency, because it uses full frequency instead of a specific frequency, and it is reinforced by the concept of distinguishing between direct and indirect relationship between signals, in addition to specifying directionality. That is, dDTF consists of full frequency directed transfer function and partial coherence, given by

$$dDTF_{ij}(f) = pCOH_{ij}(f) \cdot ffDTF_{ij}(f)$$

where ffDTF is defined in the equation with the full- frequency(ff) :

$$\text{ff DTF}_{ij}(\text{f}) = \frac{\text{H}_{ij}(\text{f})}{\sqrt{\sum_{\text{f=fl}}^{\text{fu}} \sum_{k=1}^{m} |\text{H}_{ik}(\text{f})|^2}}$$

and partial coherence(pCoh) is defined by the equation with Mij(f) indicating the minor obtained by eliminating *i* and *j* components from spectral matrix:

$$\text{pCoh} = \frac{\text{M}_{ij}(\text{f})}{\sqrt{\text{M}_{ii}(\text{f})\text{M}_{jj}(\text{f})}}$$

After dDTF results were obtained via the above equation, brain cortical areas identified by dDTF were compared with the resection areas in Group A and with the postoperative EEG in Group B. The concordance of the areas identified by dDTF with the resective areas in Group A and with the areas for epileptogenic discharges on postoperative EEG in Group B was evaluated as either hemispheric lateralization or lobar localization.

4. Statistical significance of causality

To make deductions about causality, I applied surrogate data as nonparametric statistical significance test. Surrogate data were utilized to compare values between signals and to estimate the expected probability for dDTF under the null hypothesis of no causality. I permuted the shuffling and causality process 250 times for each source in the time series to deduce a reasonable estimate. I applied a permuted significant value of $p<0.05$ and used the False discovery rate as a correction for multiple comparisons[21].

The chi-squared test, Fisher's exact test and the Mann-Whitney test were used to determine the differences between Group A and Group B, and p- values < 0.05 were considered significant.

III. RESULTS

1. Clinical characteristics of patients

All patients had GSW which did not show localization or lateralization on preoperative EEG. In Group A, all patients had complete or partial agreement for the primary epileptogenic zone as determined via presurgical evaluation. In Group B, all patients had no agreement for the localized primary epileptogenic zone and underwent corpus callosotomy as a palliative surgical treatment, and who had bilateral independent epileptogenecity after corpus callosotomy. Clinical differences between group A and B were not statistically significant, except with regard to surgical outcome (Table 1).

Table 1. Clinical characteristics of patients with Lennox-Gastaut syndrome 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 (%)	5 (41.7)	5 (33.3)
Surgical outcome (%)		
Good (Engel Class I or II)	12 (100.0)	3 (20.0)
Poor (Engel Class III or IV)	0	12 (80.0)

[a] Data presented as median (data range); AED , antiepileptic drug; F/U, follow-up

2. Source localization for generalized sharp and wave discharges

Group A had a cluster of components including resected areas and medial

frontal area, and Group B had a cluster of components on multifocal and medial frontal areas using ICA (Fig. 1).

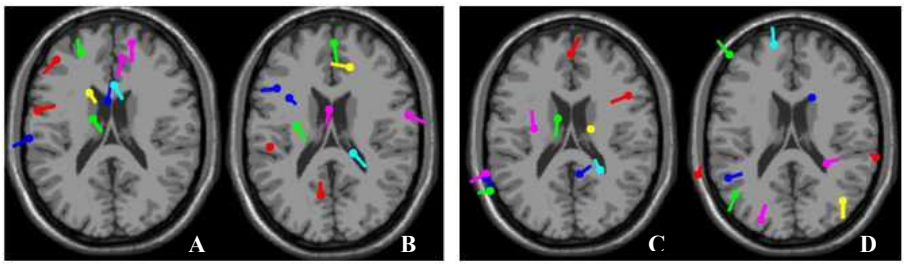

Figure 1. The cluster of components detected by independent component analysis (ICA). A, B) The cluster of components by ICA, including the resected areas and medial frontal area, in 12-year-old female patient in Group A who underwent left hemispherotomy with Engel Class I (A: awake state, B: asleep state) C, D) The cluster of components including multifocal and medial frontal areas in a 11-year-old male patient in Group B who underwent callosotomy only with Engel Class I (C: awake state, D: asleep state)

3. dDTF results compared to resective areas or postoperative EEG

The results of dDTF for each group after ICA application were revealed in Table 2 and Table 3. In Group A, the results of dDTF in all patients included resective areas, and in Group B, they included bilateral or multifocal areas. The extent of the resective areas was wider than that found via dDTF, and each area was confirmed by pathologic finding in Group A.

Table 2. Primary epileptogenic zone identified by dDTF in Group A during the awake and the asleep states

Sex/ Age	MRI results	Site for dDTF during awake state	Site for dDTF during asleep state	Resection site	Pathology
M/9	Normal	Rt.F, P, T	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. basal ganglia	Lt. H	Polymicro -gyria
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 cerebromalcia	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

CD, cortical dysplasia; CM, carvenous malformation; FCD, focal cortical dysplasia; Rt., right; Lt., left; F, frontal; P, parietal; T, temporal; O, occipital; NPD, no pathological diagnosis

Table 3. Primary epileptogenic zone identified by dDTF in Group B during the awake and the asleep states

Sex/ Age	MRI results	Site for dDTF during awake	Site for dDTF during asleep	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	Lt.F	Both F	IV
M/9	Pachygyria	Lt.F, Rt.O	Lt.F, O, Rt. O	Both F, Rt.C	IV
F/6	Mild atrophy	Lt.T,O, Rt. F	Lt. P,O, Rt.F	Both F, T, O	IV
M/8	Ventriculomegaly	Lt.T, Rt.F	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	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, Both BG	Rt. thalamus Rt.F, Lt. T	Both F,T	II
F/18	Normal	Rt.F	Lt.F, Rt.F	Both F	IV

Rt., right; Lt., left; F, frontal; P, parietal; T, temporal; O, occipital; PV, parietal vertex; FV, frontal vertex; H, hemisphere; BG, basal ganglia

In an analysis of GSW during each awake recording (Fig. 2) and asleep recording (Fig. 3), dDTF confirmed the primary epileptogenic zone which contributing to forming GSW regardless of resective surgery.

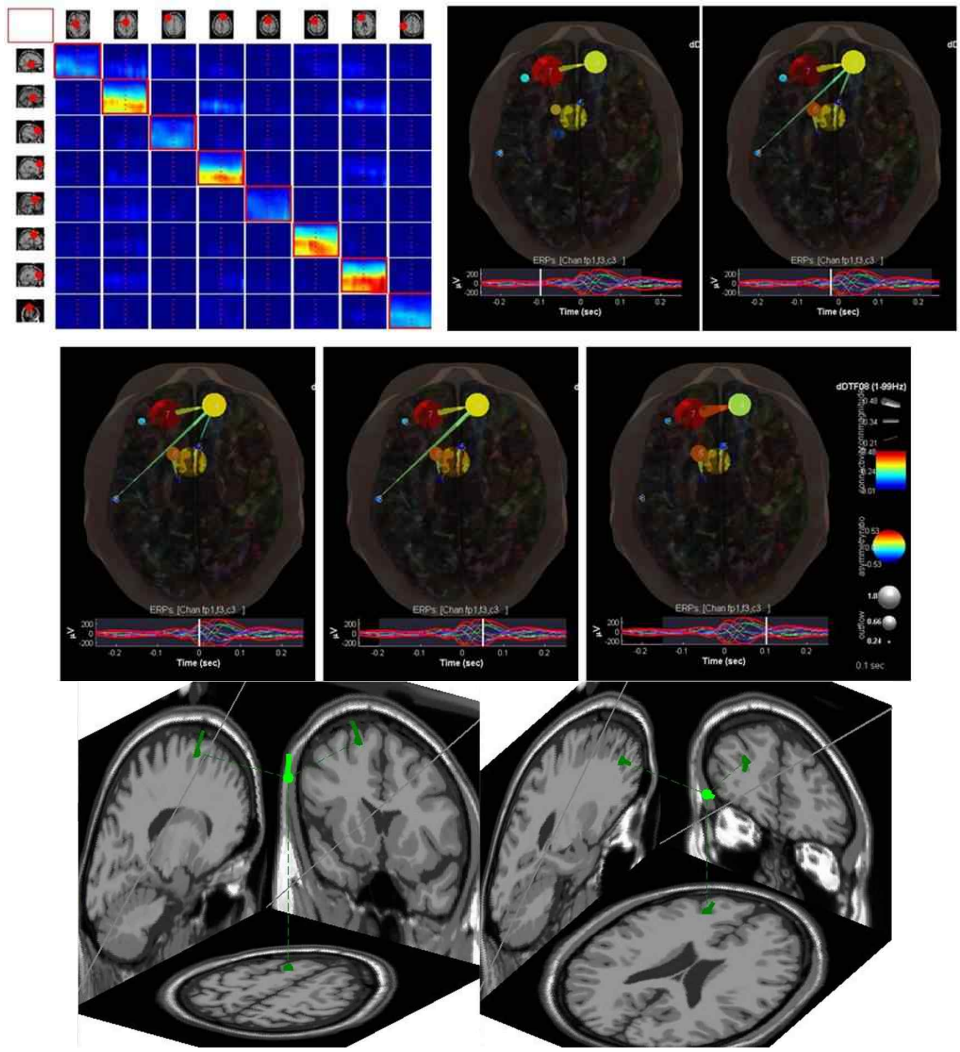

Figure 2. Directional causality of brain connectivity for generalized sharp and wave discharges during the awake state in a 12-year-old female patient in Group A who underwent left hemispherotomy with Engel class I. A) Time-frequency analysis for each component contributing generalized sharp and wave discharges (time series:-0.2~0.2, frequency 0-99 Hz) with maximal frequency 0-3 Hz. B-F) 3 dimensions simulation of directional causality for each source activity. The components of number 6 and 7 present electrical source activities. The flow of the component of number 7 is transferred to number 4, and which is

transferred to number 2 with times series at -0.1, -0.03, 0, 0.05 and 0.1 second. The components of number 6 and 7 are predicted to be the primary epileptogenic zone at the start of generalized sharp and wave discharges. G) The component of number 6 component, which is localized at the left superior frontal gyrus. H) The component of number 7, which is localized at the middle frontal gyrus. Brain connectivity is statistically significant at $p < 0.05$.

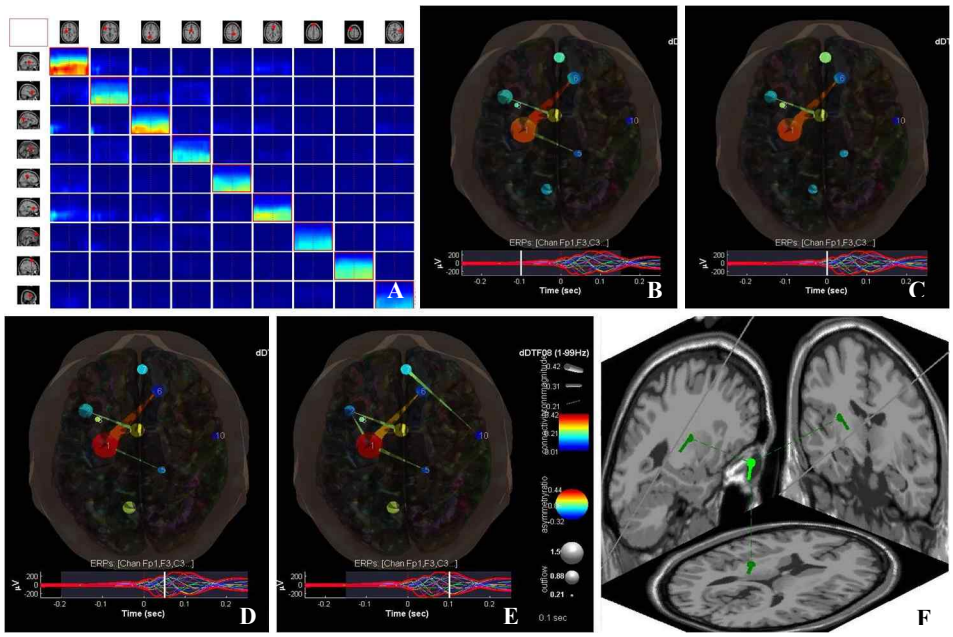

Figure 3. Directional causality of brain connectivity for generalized sharp and wave discharges during the asleep state in a 12-year-old female patient in Group A who underwent left hemispherotomy with Engel class I. A) Time-frequency analysis for each component contributing to generalized sharp and wave discharges (time series:-0.2~0.2, frequency: 0-99 Hz) with maximal frequency 0-3 Hz. B-E) 3 dimensions simulation of directional causality for each source activity with times series at -0.1, 0, 0.05 and 0.1 second. The component of number 1 is predicted to be the primary epileptogenic zone at the start of generalized sharp and wave discharges. F) The component of number 1

component, which is localized at the left basal ganglia. Brain connectivity is statistically significant at $p < 0.05$.

The localization of dDTF was identified at only one area in four patients in Group A, and the localization result was concordant within resective areas in these patients. The number of localization was identified at less than three areas in most of Group A, while more than three areas in most of Group B (Table 4).

Table 4. The number of localization by dDTF in Lennox-Gastaut syndrome

Number of localization by dDTF	Group A	GroupB
1	4	
2	3	5
3	5	6
≥ 4		4

($p<0.05$)

In Group A, the dDTF results usually showed lateralization or localization (83.3%). In contrast, bilateral or multifocal areas were predominant in Group B (93.3%) ($p<0.001$). Areas identified by dDTF in 58.3% of Group A were included in the resective areas. However, the results of dDTF were localized at resective areas in all patients, even though the areas detected by dDTF included other areas (Table 5). These discordant results of dDTF were primarily due to the localization of frontal areas. These results might mean that frontal areas contributed to the generation of spikes from the epileptogenic zone via thalamocortical circuits, as frontal area was localized at 91.7% of Group A. Surprisingly, dDTF results showed the high concordance in 14 patients (93.3%) when compared to the areas of epileptiform discharges on postoperative EEG in Group B.

Table 5. The concordance rate of the cortical epileptogenic zone identified by dDTF when compared to the resection site in Group A and to postoperative EEG after callosotomy in Group B

	Concordance rate (%)
Primary epileptogenic zone by dDTF in Group A (N=12)	
within resective areas only	7 (58.3)
within resective areas + ipsilateral independent area	3 (25.0)
within resective areas + contralateral independent area	2 (16.7)
Primary epileptogenic zone by dDTF in Group B (N=15)	
Unilateral or localized areas	1 (6.7)
Bilateral or multifocal areas	14 (93.3)

($p<0.001$)

Among areas identified by dDTF, the frontal area was localized in 11 patients (91.7%) in Group A (Table 6) and 15 patients (100 %) in Group B (Table 7), while extra-frontal areas were localized at mean 33.3% in Group A and at mean 24.5% in Group B, when midline structures were not calculated ($P>0.05$). Midline structure was localized in one patient in Group A with left hemisphere cortical dysplasia (8.3%) and in 4 patients in Group B (26.7%). Surprisingly, localization of dDTF in extra-frontal areas was concordant in laterality in all patients, as well as in localization in all patients except one in Group A.

Table 6. The location of dDTF in Group A

Location	No. of cases (%)	Concordance in laterality (%)	Concordance in localization (%)
Cortex	12		
Frontal	11 (91.7)	9 (81.8)	8 (72.7)
Temporal	6 (50.0)	7 (100)	7 (100)
Parietal	1 (8.3)	1 (100)	1 (100)
Occipital	5 (41.7)	5 (100)	4 (80.0)
Deep gray matter	1		
Basal ganglia	1(8.3)		

Table 7. The location of dDTF in Group B

Location	Number of cases (%)
Cortex	15
Frontal	15 (100)
Temporal	4 (26.7)
Parietal	3 (20.0)
Occipital	4 (26.7)
Deep gray matter	4
Basal ganglia	3 (20.0)
Thalamus	2 (13.3)

I also calculated the diagnostic sensitivity, specificity and positive predictive value of dDTF for localization and lateralization, and I found high values worth noting as potential diagnostic tools for identifying the primary epileptogenic zone (Table 8).

Table 8. Diagnostic sensitivity, specificity and positive predictive value of dDTF for lateralization and localization in Lennox-Gastaut syndrome

dDTF result	Sensitivity	Specificity	Positive predictive value
Lateralization	83.3 %	86.7 %	83.3%
Localization	62.5 %	63.2%	41.7%

IV. DISCUSSION

dDTF- based MVAR can provide rich clues to directional causality, reflecting deep epileptic neuronal networks. As yet, few studies have explored the possible superiority for dDTF- based MVAR, which has been validated in other EEG datasets by analyzing event-related electrical stimuli and by detecting sources for the generation and propagation of the epileptic discharges in a limited number of available epilepsy studies[8,14, 19,22,23]. My study suggests that the existence of localized areas, rather than different mechanism of epileptic

neuronal networks in LGS, can make resective surgery possible. The resective operable group usually showed unilateral areas for the primary epileptogenic zone, confirmed by pathologic findings, while the inoperable group showed multifocal or bilateral areas. Surprisingly, I found that the results of dDTF were localized to the resective areas in all patients in Group A, and they were well correlated with the results of postoperative EEG after corpus callosotomy in Group B. The application of dDTF- based MVAR was good enough to predict whether a patient belonged in the resective operable group.

Source activities for GSW with bilateral synchronization usually localize to frontal areas, no matter which frontal area it is for the primary or secondary GSW[3,9,10]. I found that frontal areas were the dominant areas in LGS, and they could play an important role in generating GSW because the results of dDTF were localized to frontal area as 91.7% and 100% in Group A and Group B, respectively. These results showed that frontal areas might be involved in the generation of GSW, and might also simultaneously play an important role in spreading from the epileptogenic zone and forming the GSW. One study reported that the difference between primary and secondary GSW was the localization of dipole source of the largest potential contribution to the GSW using ICA. In secondary bilateral synchronization, frontal areas for the dipole source occurred in 82.6 % of cases, while extrafrontal areas occurred in 17.4%[3]. However, dipole source using these methods might not be the primary epileptogenic zone. Because dipole source of small potential contribution to the GSW might be the primary epileptogenic zone triggering other sources, even if not largest potential contribution. In my study, frontal areas as primary epileptogenic zone were found in 91.7% and 100% of cases in Group A and Group B, respectively, while extra-frontal areas were identified as primary epileptogenic zone in 33.3% and 24.5% of cases in Group A and Group B, respectively. Especially, I found that the localization of dDTF in extra-fontal areas was superior to those in frontal areas in localization or lateralization for

identifying the primary epileptogenic areas. Thus, by using dDTF, I can detect deeper neuronal networks, as opposed to superficial networks, such as the primary epileptogenic zone triggering other areas, which can be confirmed by surgical resection and histopathology.

DTF is an appropriate tool for analyzing brain connectivity without consideration for volume conduction as well as noise or artifact, but it has weak directional causality for direct and indirect relationship. dDTF is strengthened by applying the partial coherence function without a specific frequency to identify direct relationship, and it reveals lower false causality than DTF in the EEG data[13,18,19,24]. This application of directional causality has never before reported in GSW in LGS. It is difficult to prove the hypothesis that the primary epileptogenic zone identified by directional causality is the real epileptic focus, but my study supported this hypothesis via high concordance with the resective surgical areas. Previous study for ictal onset on intracranial EEG in LGS reported that the use of dDTF was superior for identifying the primary epileptogenic zone and corresponded well with the resective areas[25]. However, source analysis to identify the primary epileptogenic zone on intracranial EEG was not analyzed in the entire brain but in the predicted areas as primary epileptogenic zone. This finding was to be difficult to use for guiding or substituting intracranial monitoring, even if validation was for DTF only, unlike in the present study. Wilke et al.[26] also reported that epileptogenic foci corresponded well with source activities identified by DTF for interictal spikes on electrocorticography in focal epilepsy. Contrary to the previous study, my study showed that the analysis for interictal GSW using dDTF on scalp EEG enabled identifying the primary epileptogenic zone in LGS. Furthermore, in focal cortical dysplasia, source localization of interictal spikes on scalp EEG associated with the epileptogenic zone over visible areas on MRI, and contributed to epileptogenic zone as well as remote areas suggesting network organization[27]. Thus, source for interictal spikes might also be independent

multiple epileptogenic foci or one epileptogenic focus spreading to another remote areas. My results using directional causality could indicate either independent multiple foci or one epileptogenic focus spreading to another remote areas[26,27]. Interictal spikes are visible as GSW in LGS, but primary epileptogenic zone may be hidden in GSW and can be detected by source analyses such as directional causality.

EEG shows superior temporal resolution but limited spatial resolution. To overcome this drawback, I used dDTF- based MVAR to better reveal the primary epileptogenic zone spatially. However, my data still exhibit limited spatial resolution because I used the 10-20 international system. To provide more accurate spatial resolution, dense array EEG can be used with over 100 channels. Source estimation for interictal spikes of dense array EEG using 256-channel produced similar results compared with the areas of seizure onset and the interictal spike on intracranial EEG, and might be able to reduce the need for invasive intracranial EEG in neocortical epilepsy[28]. If this dense array EEG were applied, I would obtain more accurate spatial as well as temporal resolution for directional causality and avoid invasive intracranial monitoring. Further research on directional causality is needed to understand the epileptic neuronal network using dense array EEG in LGS.

V. CONCLUSION

In conclusion, dDTF of generalized sharp and wave discharge is valuable for identifying the primary epileptogenic zones in LGS. Further study of dDTF is required to determine the underlying pathogenesis of the epileptogenic zone generating secondary generalized epileptic encephalopathy.

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< ABSTRACT (IN KOREAN)>

레녹스 가스타우트 증후군에서의 일차 간질 병소를 찾는데 있어 dDTF 의 역할

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서론: 난치 뇌전증에서 일차 간질 병소를 찾아낼 수 있다면 그 부분을 절제함으로써 환자는 경련으로부터 자유로울 수 있다. 그러나 레녹스 가스타우트 증후군의 경우, 여러 진단 도구를 이용함에도 불구하고 일차 병소를 찾아내는 것은 매우 어렵다. 그래서 우리는 수술적 치료를 시행했던 레녹스 가스타우트 환자들을 대상으로 전신 예파를 분석함으로써 일차성 간질 병소를 찾아내고자 하였다. 또한, 일차 간질 병소가 제거된 환자군과 일차 간질 병소를 찾을 수 없어 고식적 수술을 시행한 환자군 간에 있어 병소에 대한 차이점이 있는지에 대해서도 연구하고자 하였다.

방법: 2005년에서 2013년까지 우리는 수술적 치료를 시행한 레녹스 가스타우트 환자들을 대상으로 하였다. 이들 중 병소 절제술을 하고 수술에 대한 발작의 예후가 좋은 12명의 환자를 A 그룹으로 분류하였고 간질 병소를 찾지 못하여 고식적인 수술인 뇌량 절제술을 시행한 17명의 환자를 B 그룹으로 분류하였다. 수술적 치료를 시행하기 이전의 뇌파를 이용하여 수면과 각성 상태를 각각 10분씩 선택하여 direct directed transfer function(dDTF)을 이용하여 전신 예파를 분석하였다. 먼저 independent component analysis를 통하여 전신 예파의 형성에 기여하는 소스를 찾아 낸

후, 일차 간질 병소를 찾기 위해 dDTF 방법을 사용하였다.
결과: 그룹 A 의 dDTF 결과에서 편측화 소견을 83.3 %에서 보였으며 그룹 B 에서는 양측화 소견을 93.3%에서 보였다. 그룹 A 에서 dDTF 결과는 모두 절제 병소를 포함하였다. 그룹 B 에서는 dDTF 결과가 뇌량 절제술 후 뇌파 소견과 비교하여 93.3%에서 합당한 소견을 보였다. dDTF를 이용하여 일차 간질 병소를 확인하는데 있어 편측화에 대한 민감도는 71.4%, 특이도는 86.%, 양성예측치는 83.3%였으며 국소화에 대한 민감도는 62.5%, 특이도는 63.2%, 양성예측치는 41.7% 였다.
결론: dDTF를 이용하여 전신 극파를 분석하는 것은 레녹스 가스타우트 증후군 환자에 있어 여러 진단도구와 더불어 일차 간질 병소를 찾아내는데 도움을 주어 병소 절제술 치료를 가능하게 한다.

핵심되는 말: 소스 분석, 레녹스 가스타우트 증후군, 전신 극파