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Predictive role of brain connectivity for resective surgery in Lennox–Gastaut syndrome

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HIGHLIGHTS

- Laterality by causal connectivity was concordant with post-callosotomy EEG.
- The areas by direct directed transfer function (dDTF) showed high concordance in patients with good surgical outcome.
- The use of causal connectivity can be helpful in deciding on resective surgery in LGS.

ABSTRACT

Objective: Callosotomy can reveal hidden primary epileptogenic areas in Lennox–Gastaut syndrome (LGS). We studied the significance of causal connectivity for identifying hidden epileptogenic areas in preoperative electroencephalography (EEG) and for making a decision regarding resective surgery.
Methods: We enrolled 18 LGS patients who underwent corpus callosotomy. Eight patients with unilateral epileptogenicity on post-callosotomy EEG underwent resective surgery (group A). Ten patients with independent bilateral epileptogenicity did not undergo resective surgery (group B). We analyzed generalized epileptiform discharges on pre-callosotomy EEG via direct directed transfer function (dDTF) and partial directed coherence (PDC).
Results: All regions exhibiting unilaterality in group A and bilaterality identified by dDTF or PDC in group B were concordant with the lateralization of the irritative zone on post-callosotomy EEG and with the localization of the resective areas, except for one patient in group A. The regions identified by dDTF exhibited high concordance rates with the resective areas in patients with good outcomes.
Conclusions: Causal connectivity methods showed good concordance with hidden epileptogenic areas, and its concordance was associated with the prognosis of surgical outcome.
Significance: This study provides evidence that causal connectivity methods can be helpful in deciding which type of surgery will be suitable for an LGS patient.

1. Introduction

Lennox–Gastaut syndrome (LGS) is a syndrome-specific disorder caused by multiple etiologies. LGS characterizes multiple types of seizure, developmental deterioration, and specific electroencephalographic (EEG) features that include bilaterally synchronized generalized sharp and wave discharges (GSWs). These GSWs may hide the primary epileptogenic areas (PEAs) due to the propagation of activity from the PEA to the contralateral hemisphere or due to buildup with synchronous electrical firing from independent bilateral epileptogenic foci via the corpus callosum or subcortical structures (Jung et al., 2005; Ono et al., 2009; Lin and Kwan, 2012). Therefore, these discharges may provide a clue of the underlying brain pathologies, such as cortical dysplasia. Corpus callosotomy reveals PEAs by disrupting GSWs, and it can induce changes in electrical activity, blood flow, and metabolism in the lesion (Ono et al., 2009; Lin and Kwan, 2012;

Abbreviations: LGS, Lennox–Gastaut syndrome; GSW, generalized sharp and wave discharges; PEAs, primary epileptogenic areas; MVAR, multivariate autoregressive modeling; PDC, partial directed coherence; dDTF, direct directed transfer function; ICA, independent component analysis; DTF, directed transfer function; pCoh, partial coherence.

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Hur et al., 2011). A previous study suggested that bilateral cortical epileptogenesis could exist with asymmetrical susceptibility, although callosal compound action potentials exhibited no difference in conduction time between an altered and an unaltered group after corpus callosotomy (Ono et al., 2002). With changes in cortical epileptogenicity, corpus callosotomy is clinically relevant to determine whether the hidden PEA is present unilaterally or bilaterally. This clue facilitates decisions concerning resective surgery to control seizures and to improve the quality of life, even though the PEA is rarely identified in LGS without focal lesions (Ono et al., 2009; Hur et al., 2011).

However, GSW itself does not reveal the PEA. To identify the PEA for GSWs, computational analyses have been rapidly developed in the field of epilepsy. Among computational analytic methods, causal connectivity based on multivariate autoregressive modeling (MVAR) overcomes the limitations of bivariate autoregressive methods and identifies the directionality of pathways (Korzeniewska et al., 2003; Kuś et al., 2004). In particular, partial directed coherence (PDC) and direct directed transfer function (dDTF) have been proven to produce low fictitious results with respect to the relationships and directionality between indirect and direct pathways of several source signals (Baccalá and Sameshima, 2001; Korzeniewska et al., 2003; Fasoula et al., 2013). In addition, these methods are promising for the differentiation of source signals on event-related EEG data and on the propagation of interictal spikes in both generalized epilepsy and focal epilepsy (Sitnikova et al., 2008; Lin et al., 2009; Wilke et al., 2009, 2010; Pulsipher et al., 2011; Varotto et al., 2012).

We investigated the sources obtained by causal connectivity to analyze GSWs of real multichannel EEG data and to identify hidden PEAs. We also studied the possible predictive role of the causal connectivity method in surgical decisions regarding palliative or curative surgery.

2. Materials and methods

2.1. Patients

LGS patients who had undergone corpus callosotomy due to absence of focal epileptogenic areas eligible for resective surgery were recruited from the epilepsy center at Severance Hospital (Seoul, Korea) between 2007 and 2013. These patients met the inclusion criteria of LGS, exhibiting multiple types of seizures, characteristic EEG features of LGS, and mental retardation. Patients who had undergone previous brain surgeries or other procedures before corpus callosotomy were excluded, because these procedures may cause electrical or spatial distortions. Patients who had undergone incomplete corpus callosotomy despite planning a complete resection were also excluded, because incomplete corpus callosotomy allows the propagation and generation of epileptic discharges via the remaining corpus callosum. Among the 18 patients who met these criteria (Fig. 1), eight patients exhibited unilateral cortical epileptogenicity on post-callosotomy EEG and underwent resective surgery to eliminate the PEA (group A). Ten patients exhibited bilateral cortical epileptogenicity on post-callosotomy EEG and did not receive resective surgery (group B).

All patients underwent presurgical evaluations, including clinical characteristics, video-EEG monitoring, magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) or positron emission tomography (PET). These evaluations did not reveal epileptogenic areas eligible for resective surgery, and all patients underwent corpus callosotomy.

A post-callosotomy EEG was performed over 4 h 3–6 months after the corpus callosotomy. EEG informed us of the decision for resective surgery because corpus callosotomy revealed the presence or absence of lateralization or localization of irritative areas. Patients who exhibited lateralization on post-callosotomy EEG underwent re-presurgical evaluation and resective surgery for epileptic foci. The resected areas were confirmed by histopathological findings, including different subtypes of focal cortical malformations according to the International League Against Epilepsy classification system (Aronica et al., 2012). Post-resective EEG was rechecked 3–6 months after resective surgery.

Surgical outcomes were determined after resective surgery in group A and after corpus callosotomy in group B using Engel's classification at a later visit to an outpatient clinic (Engel et al., 1993). Our study was approved by the institutional review board, and data analyses were performed without patient identifiers.

2.2. Data acquisition

Video-EEG monitoring was performed before corpus callosotomy using a digital EEG acquisition system (Grass Telefactor, Astro-Med Inc., West Warwick, RI, USA) over 48 h with 21 electrodes placed on the scalp. Video-EEG monitoring applied the international 10–20 system with a sampling rate of 200 Hz and a band-pass width from 0.5 to 70 Hz. GSWs not showing focal EEG features were obtained with reference to both mastoids in the EEG of both the sleep and awake states. The GSW was extracted from −500 to 500 ms, where 0 ms was set at the peak amplitude of the electrode of the frontal vertex area because the frontal cortex occupies more than two-thirds of the corpus callosum (Sitnikova et al., 2008; Hur et al., 2011; da Silva Braga et al., 2014).

To decompose GSW into the multiple independent sources after data averaging, independent component analysis (ICA) was used along the time series. The ICA algorithm using the DIPFIT plug-in (EEGLAB software toolbox for MATLAB, MathWorks, Inc. v 11.0) was applied to the localization of each source and the simulation of spatiotemporal resolution (Delorme and Makeig, 2004; Moeller et al., 2011). The DIFIT plug-in performs the reconstruction of decomposed multiple sources with spatial resolution using a standardized boundary element head model obtained from the Montreal Neurological Institute coordinates (Oostendorp and Van Oosterom, 1989). Each reconstructed source below 30% in residual variance was used in the analysis of causal connectivity. A relatively high residual variance for each reconstructed source allowed more sources and >30% in our study was plotted outside the brain (Hobson and Hillebrand, 2006).

dDTF and PDC were used as connectivity methods in the identification of PEA using reconstructed sources. Two methods were implemented in a source information flow toolbox (EEGLAB software toolbox for MATLAB, MathWorks, Inc. v 11.0) (Delorme et al., 2011). First, ensemble normalization with short windows was applied to a preprocessing step for MVAR to improve the local stationarity because ongoing oscillations revealed more considerable neuronal networks than mere analysis for event-related potentials. A time window of 500 ms was selected with a stepwise advance of 10 ms. Frequency was chosen with the range of maximal power spectral density (0.5–35 Hz) in time–frequency transforms of components (EEGLAB software toolbox for MATLAB, The Math Works, Inc. v 11.0) for each patients. Sources identified by dDTF and PDC were obtained using a time–frequency grid and simulated by three-dimensional brain movies. The sources obtained by dDTF and PDC were compared to the resected areas or irritative areas on post-callosotomy EEG.

2.3. dDTF and PDC estimators as causal connectivity

Coherence analysis does not provide information on causal directionality including a direct and indirect pathway between