www.surgicalneurologyint.com

ScientificScholar® Knowledge is power
Publisher of Scientific Journals

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Epilepsy

Editor
Warren Boling, MD
Loma Linda University Medical Center, Loma Linda, CA, USA

SNI® Open Access

*Case Report*

# Intraoperative epileptogenic network visualization using gamma oscillation regularity correlation analysis in epilepsy surgery

Yuta Kobayashi, Yosuke Sato, Tatsuya Sugiyama, Tohru Mizutani

Department of Neurosurgery, Showa University School of Medicine, Tokyo, Japan.

E-mail: Yuta Kobayashi - 11112041m@gmail.com; *Yosuke Sato - yanda2011@gmail.com; Tatsuya Sugiyama - tasugiyama-nsu@umin.org; Tohru Mizutani - mizutani.nsutky@gmail.com

***Corresponding author:**
Yosuke Sato,
Department of Neurosurgery,
Showa University School of Medicine, Tokyo, Japan.

yanda2011@gmail.com

Received : 21 March 2021
Accepted : 29 April 2021
Published : 07 June 2021

**DOI**
10.25259/SNI_298_2021

**Quick Response Code:**

## ABSTRACT

**Background:** We have recently demonstrated that gamma oscillation (30–70 Hz) regularity (GOR) analysis accurately localized epileptogenic focus using intraoperative electrocorticographic data. In this report, we assessed whether GOR correlation analysis could depict epileptogenic networks intraoperatively. Dual foci in temporal lobe epilepsy without hippocampal structural abnormalities are difficult to diagnose. Using our GOR correlation analysis, we aimed to intraoperatively visualize such dual foci and epileptogenic networks.

**Case Description:** A 56-year-old man suffered from pharmacoresistant focal impaired awareness seizures. Magnetic resonance imaging demonstrated an 8 × 12-mm cavernoma in the right inferior temporal gyrus without any structural changes in the hippocampus. Since ictal semiology indicated a high probability of epileptogenicity in the right hippocampus, we reached the hippocampus using a transsylvian approach and assessed intraoperative GOR correlation analysis in the lateral temporal lobe where the cavernoma was located and the hippocampus, simultaneously. High GORs suggestive of epileptogenicity were identified in both the lateral temporal lobe and the hippocampus. Furthermore, they were connected using GOR correlation networks. When the high GOR locations in the lateral temporal lobe and the cavernoma were removed, high GORs and those networks were found within the hippocampus only. After additional hippocampal transection, high GORs and these networks were absent. The patient became seizure-free after the surgery.

**Conclusion:** Our GOR correlation analysis may be a powerful tool for intraoperative evaluation of epileptogenic networks in epilepsy surgery.

**Keywords:** Cavernoma, Dual pathology, Epileptogenic network, Gamma oscillation regularity, Sample entropy, Temporal lobe epilepsy

## INTRODUCTION

We have previously demonstrated that gamma oscillation regularity (GOR) in electrocorticographic (ECoG) data is strongly related to epileptogenicity and that quantifying the GOR using sample entropy analysis allows for epileptic focus visualization and detailed algorithms.[8,9] In focal epilepsy, distant brain structures are functionally connected by abnormal synchronization, and epileptogenic networks are formed hierarchically.[1] Although various methods have been reported to depict epileptic networks using stereo electroencephalography (EEG) signal analysis,[2] simultaneous EEG-functional magnetic resonance imaging,[11] and magnetoencephalography,[3] there has never been an intraoperative visualization of epileptogenic networks using ECoG data. It has been reported that functional connectivity analysis, in which time-series correlations in EEG data are calculated and those with high correlations are considered to be "functionally" connected, is effective as a network analysis.[4,15] In this context, we hypothesized that the epileptogenic areas with significantly high GOR would be connected to each other as epileptogenic networks with a high time-series correlation of GOR. Here, we report the successful intraoperative visualization of epileptogenic networks connecting the lateral temporal lobe to the ipsilateral hippocampus using GOR correlation analysis of ECoG data in a patient with dual foci in temporal lobe epilepsy.

## CLINICAL PRESENTATION

A 56-year-old man had intractable epileptic seizures for more than 3 years. His symptoms included motor automatisms (hand movements) of focal impaired awareness seizures. Brain MRI revealed a cavernoma measuring 8 × 12 mm in the right inferior temporal gyrus. Neither reduced hippocampal volume nor enlarged temporal horn, which is a typical structural finding of mesial temporal lobe epilepsy, could be seen in fluid-attenuated inversion recovery sequence images [Figure 1a]. Iomazenil-single-photon emission computed tomography showed decreased accumulation in the right mesial temporal lobe [Figure 1b]. Interictal EEG showed spikes in F8 and T4. As seen in the dense array EEG, the spikes originated in the right temporal lobe, but it was unclear whether they were mesial or lateral type. Since ictal semiology indicated a high probability of epileptogenicity in the mesial temporal lobe, hippocampal resection was considered necessary in addition to cavernoma resection.

Under general anesthesia, the body was placed in the supine position, and the head position was fixed with a rotation of 30° to the left side. We placed the 2 × 4 strip electrodes (Unique Medical Co., Ltd., Tokyo, Japan) on the right temporal lobe where the cavernoma lesion was well covered, and the 1 × 4 strip electrodes on the hippocampus, using a transsylvian approach. We obtained ECoG recordings and performed GOR correlation analysis (1) before resection, (2) after cavernoma resection, and (3) after hippocampal transection, respectively. In hippocampal transection, the hippocampal head to the hippocampal tail was cut subpially toward the dorsal side of the hippocampus, and the parahippocampal gyrus was dissected from the innominate sulcus. Postoperative brain MRI showed complete resection of the cavernoma and hippocampal transection [Figure 1c]. The patient had no postoperative neurological deficits and was seizure-free after 6 months of follow-up.

### ECoG data recordings

The ECoG data were recorded using a Nihon Kohden Neurofax EEG system (Nihon Kohden, Tokyo, Japan) with a bandpass filter from 0.16 to 300 Hz with a sampling rate of 1 kHz. A 60-Hz notch filter was applied to all channels, and the sensitivity was between 30 and 100 μV/mm according to the amplitudes of the background activities and epileptic discharges. The recordings were obtained using a reference electrode placed on the forehead. All selected ECoG epochs were inspected to ensure that they were not contaminated by artifacts.

### GOR correlation analysis

The detailed algorithm for GOR analysis using the sample entropy method was described in our previous studies.[6] In each step of the GOR correlation analysis, we selected 2-min ECoG data without any significant artifacts. The ECoG data were down-sampled to 200 Hz, where the timescale factor $\tau$ = 3–7 corresponded to the gamma frequency (28.6–66.7 Hz). We defined the GOR as the average score with $\tau$ = 3–7. Then, the time series GOR was obtained by sweeping the 20-s analysis interval by 0.5 s over the entire 2 min (i.e. 201 time

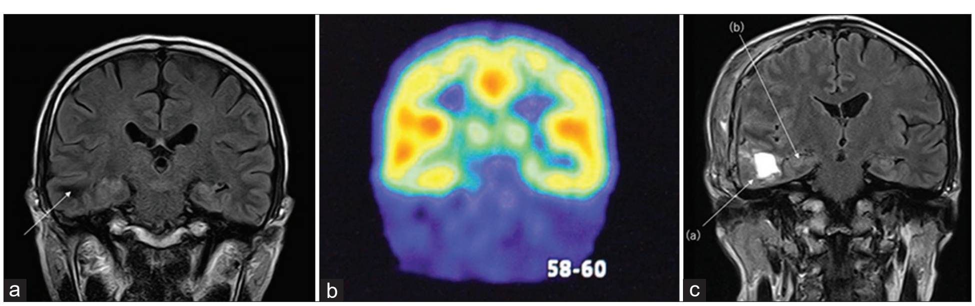


**Figure 1:** (a) Pre-operative MRI of coronal section. Fluid-attenuated inversion recovery sequence revealed 8 × 12 mm cavernoma in the right inferior temporal gyrus (arrow). Neither reduced hippocampal volume nor enlarged temporal horn, which are typical structural findings of mesial temporal lobe epilepsy, could be seen. (b) Iomazenil-single-photon emission computed tomography showed decreased accumulation in the right mesial temporal lobe (c) The postoperative brain MRI showed complete resection of cavernoma (a) and hippocampal transection (b).

series GOR). The correlation coefficient $r_{ij}$ for the time series GOR at electrodes i and j is defined as

$$r_{ij} = \frac{S_{ij}}{S_i S_j}$$

$S_{ij}$ is the covariance of electrodes i and j, and $S_i$ is the standard deviation of electrode i. In the network diagram, the threshold was set to 0.7 in this case. The edge was placed between node i and node j when $r_{ij} \geq 0.7$. We weighted the threshold between 0.7 and 1 linearly with the thickness of the edge. To visually assess the GOR, we color-coded the average GOR over 2 min. These procedures were performed using a custom program developed in cooperation with EFken Inc., Tokyo, Japan.

## RESULTS

We performed ECoG recordings and GOR correlation analysis simultaneously in the lateral temporal lobe and hippocampus. Before resection, the ECoG showed synchronized spikes in the lateral temporal lobe and hippocampus and isolated spikes in the hippocampus [Figure 2a]. The GOR was significantly high in both the lateral temporal lobe and hippocampus. Furthermore, they were connected using GOR correlation networks [Figure 2b]. After cavernoma resection from the area with significantly high GOR, the ECoG showed that spikes in the lateral temporal lobe had disappeared, and only hippocampal spikes remained behind [Figure 2c]. Significantly high GORs and these networks were found only within the hippocampus [Figure 2d]. Based on these results, we determined that hippocampal transection was required in the patient. After additional hippocampal transection, the ECoG showed that spikes in the hippocampus disappeared [Figure 2e]. The GOR was decreased in the hippocampus, and the networks were absent [Figure 2f].

## DISCUSSION

Arriving at a decision on which cerebral regions produce seizures is important in epilepsy surgery. This enables us to plan a detailed surgical strategy, which leads to excellent postoperative outcomes and minimal neurological deficits. Intraoperative ECoG has been widely used to localize epileptic activity for the management of cavernomas presenting with drug-resistant epilepsy.[5,7,12,14] However, especially in temporal cavernomas, the hippocampus may acquire secondary epileptogenicity at a distance from the cavernoma lesion. In dual foci with two epileptogenic lesions, as in the present case, the possibility of not removing the epileptogenic lesion during operation is high, which may lead to a poor seizure outcome. Recently, it has been said that "focal" epilepsies are not, in fact, so focal and involve epileptogenic networks of varying scales.[1] The concept of epileptogenic networks has been progressively introduced as a model to describe the complexity of seizure dynamics. The epileptogenic zone is referred to as a "hub," which has many epileptogenic networks with other neurons. When a seizure occurs, the hub recruits more distant neuronal networks and constitutes complex oscillatory circuits, which can be detected by ECoG.[10] Based on this concept, accurate evaluation of not only the epileptogenic zone but also the epileptogenic networks is essential for the postoperative management of epilepsy. Hence, our method can be a highly useful intraoperative diagnostic tool.

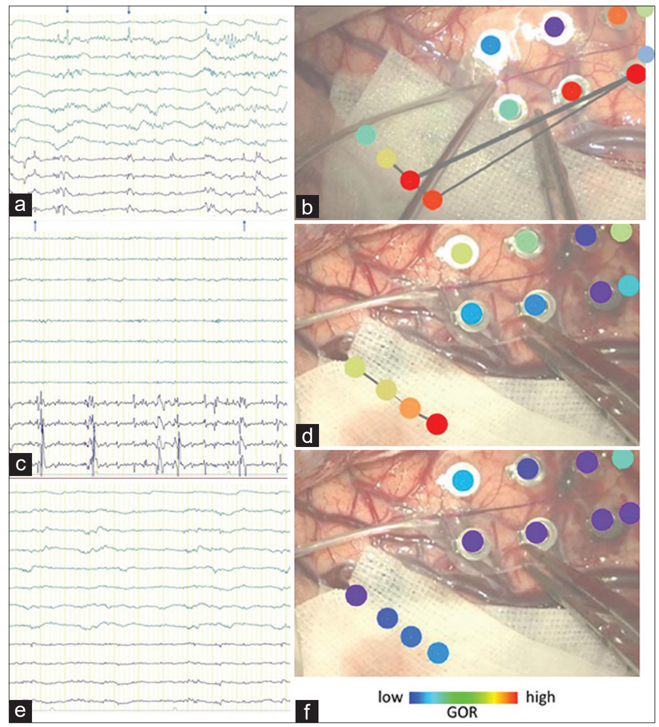


**Figure 2:** (a) Electrocorticography (ECoG) before cavernoma resection. The upper eight lows are the 2 × 4 strip electrodes on the right temporal lobe, the lower 4 lows are the 1 × 4 strip electrodes on the right hippocampus. ECoG showed synchronized spikes (↓) in the lateral temporal lobe and hippocampus, and isolated spikes (↑) in the hippocampus. (b) Intraoperative photograph of the brain surface before cavernoma resection. Upper: The right six dots are the 2 × 4 strip electrodes, and the lower-left four dots are the 1 × 4 strip electrodes. They are colored using a gamma oscillation regularity (GOR) map. The red dotted circle in the GOR map shows the area with a significantly high GOR, while the blue dotted circle in the GOR map shows the area with a low GOR. Both electrodes exhibited a high GOR. The lines connecting the dots show the electrical network analyzed by the GOR. (c) ECoG after cavernoma resection. The negative spikes in the 2 × 4 strip electrodes disappeared. On the 1 × 4 strip electrodes, synchronized positive spikes disappeared, but a negative spike remained. (d) Intraoperative photograph of the brain surface after cavernoma resection. The 2 × 4 strip electrodes showed decreased GOR, whereas a high GOR remained in the 1 × 4 strip electrodes. Networks were found only in the hippocampus. (e) ECoG after cavernoma resection. The negative spikes observed in the 1 × 4 strip electrodes disappeared. (f) Intraoperative photograph of the brain surface after hippocampal transection. The GOR decreased in the hippocampus, and the network was absent.

Video EEG monitoring can reveal the correlation between semiology and ictal EEG. The limitation of this method is that the ictal stage is the only stage in which the seizure onset zone can be detected, and waiting time for seizures is needed. Our GOR analysis requires only a few tens of seconds or at most a minute of interictal EEG data and can be used intraoperatively.[8,9] Shortening video EEG monitoring helps to reduce patients' stress, and rapid intraoperative epileptogenic zone and network visualization also require less effort by the epilepsy surgeons.

The transsylvian approach is a basic approach for the management of mesial temporal lobe epilepsy.[16] If the epileptogenic lesion increases in size, anterior temporal lobectomy or amygdalohippocampectomy should be considered, but they are associated with postoperative worsening of memory, verbal memory decline in the dominant side, and spatial memory decline on the nondominant side. As reported by Uda *et al.*,[13] transsylvian hippocampal transection is preferred to amygdalohippocampectomy, especially in the case of mesial temporal lobe epilepsy without hippocampal atrophy or sclerosis. In the current patient, there were no imaging changes in the hippocampus and no evidence of epileptogenicity of the hippocampus, except for semiology preoperatively. The transsylvian approach to the hippocampus and simultaneous GOR analysis in the hippocampus and lateral temporal lobe resulted in localized temporal corticotomy and hippocampal transection. Although this is only a case report, the effectiveness of GOR analysis is now being demonstrated in other cases, and further studies are accordingly warranted.

## CONCLUSION

Our GOR correlation analysis is a powerful tool for intraoperative evaluation of epileptogenic networks and enables us to perform better surgery for seizure control.

### Data availability statement

The raw data supporting this article will be made available by the authors, without undue reservation.

### Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

### Financial support and sponsorship

JSPS KAKENHI Grant Number JP 20K09356.

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Bartolomei F, Lagarde S, Wendling F, McGonigal A, Jirsa V, Guye M, *et al.* Defining epileptogenic networks: Contribution of SEEG and signal analysis. Eplepsia 2017;58:1131-47.
2. Bartolomei F, Wendling F, Chauvel P. The concept of an epileptogenic network in human partial epilepsies. Neurochirurgie 2008;54:174-84.
3. Chavez M, Valencia M, Navarro V. Functional modularity of background activities in normal and epileptic brain networks. Phys Rev Lett 2010;104:118701.
4. Lachaux JP, Lutz A, Rudrauf D. Estimating the time-course of coherence between single-trial brain signals: An introduction to wavelet coherence. Neurophysiol Clin 2002;32:157-74.
5. McKhann GM, Schoenfeld-McNeill J, Born DE, Haglund MM, Ojemann GA. Intraoperative hippocampal electrocorticography to predict the extent of hippocampal resection in temporal lobe epilepsy surgery. J Neurosurg 2000;93:44-52.
6. Patil AA, Andrews RV. Nonresective hippocampal surgery for epilepsy. World Neurosurg 2010;74:645-9.
7. San-Juan D, Díaz-Nuñez IC, Ojeda-Baldéz M. Utility of electrocorticography in the surgical treatment of cavernomas presenting with pharmacoresistant epilepsy. Epileptic Disord 2014;16:245-60.
8. Sato Y, Ochi A, Mizutani T, Otsubo H. Low entropy of interictal gamma oscillations is a biomarker of the seizure onset zone in focal cortical dysplasia Type II. Epilepsy Behav 2019;96:155-9.
9. Sato, Y, Wong, SM, Iimura, Y, Ochi, A, Doesburg, SM, Otsubo H. Spatiotemporal changes in regularity of gamma oscillations contribute to focal ictogenesis. Sci Rep 2017;7:9362.
10. Stefan H, Da Silva FH. Epileptic neuronal networks: Methods of identification and clinical relevance. Front Neurol 2013;4:8.
11. Thornton R, Vulliemoz S, Rodionov R. Epileptic networks in focal cortical dysplasia revealed using electroencephalography-functional magnetic resonance imaging. Ann Neurol 2011;70:822-37.
12. Tripathi M, Garg A, Gaikwad S. Intraoperative electrocorticography in lesional epilepsy. Epilepsy Res 2010;89:133-41.
13. Uda T, Morino M, Ito H, Minami N, Hosono A, Nagai T, *et al.* Transsylvian hippocampal transection for mesial temporal lobe epilepsy: Surgical indications, procedure, and postoperative seizure and memory outcomes. J Neurosurg 2013;119:1098-110.
14. van Gompel JJ, Rubio J, Cascino GD, Worrell GA, Meyer FB. Electrocorticography-guided resection of temporal cavernoma: Is electrocorticography warranted and does it alter the surgical approach? J Neurosurg 2009;110:1179-85.
15. Wendling F, Ansari-Asl K, Bartolomei F. From EEG signals to brain connectivity: A model-based evaluation of interdependence measures. J Neurosci Methods 2009;183:9-18.
16. Yaşargil MG, Krayenbühl N, Roth P, Hsu SP, Yaşargil DC. The selective amygdalohippocampectomy for intractable temporal limbic seizures. J Neurosurg 2010;112:168-85.

**How to cite this article:** Kobayashi Y, Sato Y, Sugiyama T, Mizutani T. Intraoperative epileptogenic network visualization using gamma oscillation regularity correlation analysis in epilepsy surgery. Surg Neurol Int 2021;12:254.