Delineation of the epileptogenic zone by Phase-amplitude coupling in patients with Bottom of Sulcus Dysplasia

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ABSTRACT

Purpose: The removal of the bottom of sulcus dysplasia (BOSD) often includes the gyral crown; however, this method has been controversial. We hypothesized that the epileptogenic zone of the BOSD does not include the gyral crown. To reveal the depth and extent of the epileptogenic zone of the BOSD, we applied the two electrophysiological modalities: (1) the occurrence rate (OR) of high-frequency oscillations (HFOs) and (2) modulation index (MI), reflecting the strength of phase-amplitude coupling between HFOs and slow oscillations.

Methods: We investigated the ripples [80–200 Hz] and fast ripples [200–300 Hz]) in HFOs and MI (HFOs [80–300 Hz] and slow oscillations [3–4 Hz]). We opened the sulcus at the BOSD and implanted the subdural electrodes directly over the MRI visible lesion. All patients (n = 3) underwent lesionectomy and the gyral crown was preserved.

Results: Pathological findings demonstrated focal cortical dysplasia type IIb and seizure freedom was achieved. The OR of the HFOs was not significantly different between the BOSD and the gyral crown. In contrast, the MI between HFOs and slow oscillations in the BOSD was significantly higher than that in the gyral crown.

Conclusion: High MI values distinguished the epileptogenic BOSD from the non-epileptogenic gyral crowns. MI could be a more informative biomarker of epileptogenicity than the OR of HFOs in a subset of patients with the BOSD.

Introduction

The complete removal of the bottom of sulcus dysplasia (BOSD) leads to good seizure outcomes [1]. However, it has been controversial whether the epileptogenic zone encompasses only the BOSD, or if the gyral crown is included [2]. This controversy needs to be resolved because the BOSD may exist near an eloquent area, and the resection margins should be properly delineated. However, only few reports exist on the epileptogenicity of the BOSD based on electrophysiological analysis. High-frequency oscillations (HFOs) are potential markers for epileptogenicity [3]. Interictal HFOs are mainly generated from the BOSD, however, there was no correlation between the distance from the BOSD and the rate of HFOs [4]. Another biomarker for epileptogenicity is the phase-amplitude coupling (PAC) focuses on couplings between HFOs and slow oscillations [5]. PAC is more useful for the localization of an epileptic focus than the rate of HFOs [6]. PAC between HFOs and 3–4 Hz could be a biomarker for epileptogenicity in epileptic spasms [7]. To reveal the depth and extent of the epileptogenic zones of the BOSD, the sulcus at the focal cortical dysplasia (FCD) location was opened and the grids were implanted directly on the MRI visible regions. This study aimed to determine if the epileptogenic zone is in the BOSD by analyzing the HFOs and PAC. We tested the hypothesis that the epileptogenic zone is in the BOSD, not in the gyral crown, analyzing HFOs and PAC.

Methods

The ethics committee of Juntendo University approved this study (No.16–163). Written informed consent was obtained from the patients and their parents.

Patients with drug-resistant epilepsy with the BOSD at Juntendo University Hospital were retrospectively included. The inclusion criteria were as follows: (1) an MRI visible lesion was located at the bottom of sulcus adjacent to an eloquent area (Fig. 1A); (2) electrodes were implanted directly on both the gyral crown and BOSD by dissecting the
sulcus (3) patients who underwent lesionectomy with preserved gyral crown (Fig. 1B); (4) patients achieved seizure freedom at least 2 years after surgery. A visual inspection of intracranial video electrocorticography (ECoG) results showed that seizure onset zones were determined to be the BOSD itself in all patients. According to the results of functional mapping, we confirmed that the area to be removed did not have any function. Three-dimensional surface images of the brain and BOSD were generated using the FreeSurfer script (https://surfer.nmr.mgh.harvard.edu) and a 3D slicer (https://www.slicer.org/). The Fieldtrip toolbox (http://www.fieldtriptoolbox.org/) co-registered the surface images with the location of the implanted electrodes [8]. The implanted electrodes were divided into three groups: (1) BOSD, (2) gyral crown and (3) outside (Fig. 1C, D, E). The “BOSD” was classified as the electrode that directly covers the BOSD. The “gyral crown” was classified as the one that covers the cortex above the BOSD, while all other electrodes were classified as the “outside”.

The intracranial video ECoG was recorded at a sampling rate of 2 kHz. HFOs on the bipolar montage were automatically detected using MATLAB [7,9]. The occurrence rate (OR) was defined as an index of the HFOs. The OR of ripples (80–200 Hz) and fast ripples (FRs; 200–300 Hz) were calculated using five 5-min ECoG epochs during slow-wave sleep, and five ORs of HFOs were acquired.

The modulation index (MI) is a parameter that reflects the strength of PAC between the HFOs and the slow oscillations. MI was calculated on the monopolar montage using the EEGLAB, Phase-Amplitude Coupling Toolbox (PACT), v.0.17 [5,7]. The MI between HFOs (ripples and FRs) and the 3–4 Hz was analyzed. Five MI values (HFOs and 3–4 Hz) were acquired by analyzing the five 5-min ECoG epochs. The ORs of HFOs and MI in this study were retrospectively analyzed; thus, the results of this study did not affect the real-time surgical decision-making.

All statistical analyses were performed using SPSS Statistics 25 (IBM Corp., Chuo-ku, Tokyo, Japan). We performed Steel-Dwass test for multiple comparisons after testing for data normality using the F test. Statistical significance was set at two sided \( p < 0.05 \).

Results

Three patients (with 15, 25 and 39 years old), one female and two males were enrolled. Patient 1 had a lesion at the bottom of the left postcentral sulcus with focal awareness seizure generated from tingling to tonic of the right upper limb. Patient 2 had a lesion at the bottom of the left precentral sulcus with focal awareness seizure characterized as twitching of the right upper limb. Patient 3 had a lesion at the bottom of the left angular sulcus with a focal impaired awareness seizure characterized as motionless staring. Histopathological examination demonstrated focal cortical dysplasia type Ib in all patients. After a median follow-up of 38 months (range, 31–44 months), all patients achieved seizure freedom. The ECoG data from 196 electrodes of the three consecutive patients (50–76 electrodes in each patient) were analyzed. The mean number of electrodes of in the BOSD group was 11.3 (range, 8–16), and the mean number of crown was 8.3 (range, 6–10).

The OR of ripples in the BOSD (6.4 ± 8.5, mean±SD) was significantly higher than that in the outside (1.5 ± 5.6) \( (p<0.01) \) (Fig. 2A). The OR of ripples in the crown (2.2 ± 6.4) was significantly higher than that in the outside \( (p<0.01) \). The OR of FRs in the BOSD (10.1 ± 20.0) was significantly higher than that in the outside (1.3 ± 7.6) \( (p<0.01) \). The OR of FRs in the crown (3.4 ± 11.6) was significantly higher than that in the outside \( (p<0.01) \) (Fig. 2B). The ORs of ripples and FRs were not significantly different between the BOSD and the crown.

MI (ripples and 3–4 Hz) in the BOSD (16.7 ± 23.3) was significantly higher than that in the crown (3.3 ± 5.7) and outside (1.7 ± 4.3) \( (p<0.01) \) (each) (Fig. 2C). MI (ripples and 3–4 Hz) in the crown was significantly higher than that outside \( (p=0.01) \). MI (FRs and 3–4 Hz) in the BOSD (1.0 ± 1.3) was significantly higher than those in the crown (0.2 ± 0.4) and outside (0.1 ± 0.3) \( (p<0.01) \) (each) (Fig. 2D). MI (FRs and 3–4 Hz) in the crown was significantly higher than that outside \( (p=0.02) \).

Discussion

This study found no significant difference in the ORs of HFOs between the BOSD and the gyral crown. Although it remains unclear whether HFOs in the gyral crown are physiological or pathological, we speculate that HFOs in the gyral crown are physiological. Physiological HFOs are usually generated from the sensorimotor-visual sites [5]. In our cases, all BOSDs were located adjacent to the sensorimotor and visual areas. To our best knowledge, this is the first study to differentiate the epileptogenicity of the BOSD from the gyral crown.

The surgical results suggested that the gyral crown was not epileptogenic. Our PAC analysis using HFOs and 3–4 Hz could differentiate epileptogenic BOSD and non-epileptogenic gyral crown. The following two theories of slow oscillation generation have been proposed: first, the slow oscillations represent cortical dysfunction. Second, slow oscillations in the cortex originate from the corticothalamic system [10]. In this study, we selected 3–4 Hz to elucidate the epileptogenicity of BOSD. Previous studies have reported that slow oscillations, 3–4 Hz, tend to couple with pathological HFOs [7,11]. However, the origin of the 3–4 Hz slow oscillations has not yet been well understood. All the cases of BOSD in our study were FCD type Ib; therefore, the BOSD had cortical dysfunction. Meanwhile, the gyral crown did not exhibit cortical dysfunction. Based on the first theory, 3–4 Hz may have been generated from the BOSD itself. On the other hand, the network propagating 3–4
However, this analysis shows great promise to elucidate the epileptogenicity of BOSD. It is challenging to do statistics with small number, however, this analysis shows great promise to elucidate the epileptogenicity of BOSD.

The limitation in this study is the lack of statistical power due to the small number of cases. It is challenging to do statistics with small number, however, this analysis shows great promise to elucidate the epileptogenicity of BOSD.

Conclusion

High MI values distinguish the epileptogenic BOSDs from the non-epileptogenic gyral crowns. MI could be a better biomarker of epileptogenicity than the OR of HFOs in a subset of patients with BOSD.

Ethical publication statement

We confirm that we have read the Journal’s position on issues involving ethical publication and affirm that this report is consistent with these guidelines.

Declaration of Competing Interest

There are no conflicts of interest to disclose.

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References

[1] Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, et al. Focal cortical dysplasia: neuroanatomical subtypes, EEG, neuroimaging and surgical outcomes in humans. Brain 2002;125:1719–32.
[2] Zhao B, Zhang C, Wang X, Wang Y, Liu C, Mo J, et al. Sulcus-centered resection for focal cortical dysplasia type II: surgical techniques and outcomes. J Neurosurg 2020;7:1–7.
[3] Holler Y, Kutil R, Klaassenbock L, Thomschewski A, Holler PM, Bathke AC, et al. High-frequency oscillations in epilepsy and surgical outcome. A meta-analysis. Front Hum Neurosci 2015;9:574.
[4] Hu WH, Zhao RT, Zhang C, Wang X, Sang L, Shao XQ, et al. Focal cortical dysplasia II-related seizures originate from the bottom of the dysplastic sulcus: a stereoelectroencephalography study. Clin Neurophysiol 2019;130:1596–603.
[5] Nomoda Y, Miyakoshi M, Ojeda A, Makeig S, Juhana S, Sood S, et al. Interictal high-frequency oscillations generated by seizure onset and eloquent areas may be differentially coupled with different slow waves. Clinical Neurophysiology 2016;127:2489–99.
[6] Weiss SA, Banks GP, McKhann Jr GM, Goodman RR, Emerson RG, Trevelyan AJ, et al. Ictal high frequency oscillations distinguish two types of seizure territories in humans. Brain 2013;136:796–808.
[7] Iimura Y, Jones K, Takada I, Shimizu I, Koyama M, Hattori K, et al. Strong coupling between slow oscillations and wide fast ripples in children with epileptic spasms: investigation of modulation index and occurrence rate. Epilepsia 2018;59:544–54.
[8] Mitsuhashi T, Sonoda M, Iwaki H, Luat AF, Sood S, Asano E. Effects of depth electrode montage and single-pulse electrical stimulation sites on neuronal responses and effective connectivity. Clin Neurophysiol 2020;131:2781–92.
[9] Akizawa T, McCoy B, Go CY, Ochi A, Elliott IM, Akizawa M, et al. Focal resection of fast ripples on extracranial intraoperative EEG improves seizure outcome in pediatric epilepsy. Epilepsia 2011;52:1802–11.
[10] Neske GT. The slow oscillation in cortical and thalamic networks: mechanisms and functions. Front Neural Circuits 2015;9:88.
[11] Nariai H, Hussain SA, Bernardo D, Motoi H, Sonoda M, Kuroda N, et al. Scalp EEG interictal high frequency oscillations as an objective biomarker of infantile spasms. Clin Neurophysiol 2020;131:2527–36.
[12] Cepeda C, Andre VM, Vinters HV, Levine MS, Mathern GW. Are cytogenic neurons and balloon cells generators of epileptic activity in pediatric cortical dysplasia? Epilepsia 2005;46(Suppl 5):82–8.

Fig. 2. OR of HFOs and MI (HFOs & 3–4 Hz) among the BOSD, the gyral crown, and the outside groups.

A The OR of ripples in the BOSD was significantly higher than that in the outside (p<0.01). The OR of ripples in the crown was significantly higher than that in the outside (p<0.01). The OR of ripples was not significantly different between the BOSD and crown.

B The OR of FRs in the BOSD was significantly higher than that in the outside (p<0.01). The OR of FRs in the crown was significantly higher than that in the outside (p<0.01). The OR of FRs was not significantly different between the BOSD and crown.

C The MI (ripples and 3–4 Hz) in the BOSD was significantly higher than those in the crown and outside (p<0.01, for each). The MI (ripples and 3–4 Hz) in the crown was significantly higher than that in the outside (p=0.01).

D The MI (FRs and 3–4 Hz) in the BOSD was significantly higher than those in the crown and outside (p=0.01, for each). The MI (FRs and 3–4 Hz) in the crown was significantly higher than that in the outside (p=0.02).