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Low entropy of interictal gamma oscillations is a biomarker of the seizure onset zone in focal cortical dysplasia type II☆

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ABSTRACT

Objective: Dynamic changes in the regularity of interictal gamma oscillations (GOs, 30–70 Hz) on intracranial electroencephalography (EEG) reflect focal ictogenesis with epileptogenic neuronal synchronization in focal cortical dysplasia (FCD). We investigated whether the regularity of interictal GOs is a biomarker of the seizure onset zone (SOZ) using multiscale entropy analysis.
Methods: We quantified the regularity of interictal GOs using intracranial EEG data from 1164 electrodes in 13 patients with FCD who were seizure-free postoperatively. The regularity of interictal GOs was quantified as entropy values. Low entropy represents high regularity. We standardized entropy values using Z values for each SOZ, resection area (RA), and the region outside the RA. The cutoff Z values, sensitivity, and specificity for detecting each area were calculated using area under the receiver operating characteristics curves (AUCs).
Results: Low Z values represent higher regularity of GOs. The cutoff Z value of ≤ -2.09 for the SOZ had a sensitivity of 100% and specificity of 97.1% (AUC $= 0.992 \pm 0.002$). The cutoff Z value of ≤ -0.12 for the RA had a sensitivity of 54.2% and specificity of 73.8% (AUC $= 0.673 \pm 0.019$). The cutoff Z value of ≥ -0.11 for the region outside the RA had a sensitivity of 73.8% and specificity of 54.2% (AUC $= 0.673 \pm 0.019$).
Conclusions: Low entropy of interictal GOs was a reliable biomarker for the SOZ. Maintained high entropy of interictal GOs may be an auxiliary biomarker for nonepileptogenic regions.
Significance: Low entropy of interictal GOs may be a biomarker for the SOZ in FCD type II.

1. Introduction

Focal epileptogenesis is closely related to the dynamic synchronization of interneuron activity [1,2]. Some studies have attempted to determine the dynamic characteristics of interneuron synchronization reflecting epileptiform activity [3,4], while others have suggested that gamma oscillations (GOs) (30–80 Hz) arise from synchronous interneuron activity [5,6]. Hence, the synchronization of epileptic interneurons could be evaluated based on the regularity of GOs.

Multiscale entropy (MSE) can be used to quantify the regularity of electroencephalography (EEG) signals on different time scales as entropy values [7]. Low entropy represents high regularity at arbitrary frequency of EEG and vice versa. Intracranial EEG findings from patients with focal cortical dysplasia (FCD) indicate that 1) the low entropy of interictal GOs is always found in the seizure onset zone (SOZ); 2) the entropy increase of preictal GOs occurs in the SOZ; and 3) the low entropy of ictal GOs tends to propagate over the resection area (RA) outside the SOZ [8].

The aim of this study was to determine whether the entropy of interictal GOs could serve as a biomarker of the SOZ by 1) quantifying the regularity of interictal GOs using MSE analysis; 2) standardizing the data as Z values; 3) comparing Z values among the SOZ, RA, and the region outside the RA; and 4) calculating the sensitivity and specificity for the detection of each area.

2. Materials and methods

2.1. Patients

We analyzed data from 13 pediatric patients (eight boys and five girls, aged 3–15 years) reported on in our previous study [8]. All patients met the following criteria: 1) magnetic resonance imaging (MRI)-

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visible FCD, 2) postsurgical histopathological diagnosis of FCD type II, and 3) postsurgical seizure outcome of class I according to the International League Against Epilepsy (ILAE) [16] classification system. This study was performed in accordance with the guidelines suggested by the Research Ethics Board at The Hospital for Sick Children. All patients or their families gave informed consent, and the study was approved by the Research Ethics Board at The Hospital for Sick Children.

2.2. EEG data recordings and selection

Subdural grids (interelectrode distance: 8–10 mm, 64–109 electrodes per patient) were placed over the FCD lesions. We analyzed data from 1164 electrodes. No depth electrodes were used. All EEG data were acquired at a sampling rate of 1 kHz and montaged with the reference electrode placed in an area from which epileptic discharges were not recorded. One typical habitual seizure was selected to determine the SOZ. One interictal epoch was extracted for each patient. Interictal epochs comprised 20 s of activity without interictal spikes during stage 1–2 nonrapid eye movement (non-REM) sleep with slow-wave EEG pattern separated by at least 1 h from any seizure onset. To secure the consistency of interictal epoch data, we randomly selected two other 20 s interictal epochs with minimal interictal spikes during stage 1–2 non-REM sleep separated by at least 1 h from any seizure onset, compared with the first interictal epoch using Bartlett's test and one-way analysis of variance (ANOVA), and confirmed that there were no significant differences among MSE score variances ($p > 0.05$) and MSE scores ($p > 0.05$). We collected data from 13 interictal epochs in all. All selected epochs were carefully inspected to ensure that they were not contaminated with artifacts.

2.3. Determination of the SOZ and the RA

Certified neurophysiologists (AO and HO) defined the SOZ as the region where the earliest ictal-related low-amplitude fast activity began during electroclinical seizures. Nine patients had one electrode for the SOZ, and four patients had two electrodes for the SOZ. The number of SOZ electrodes was 17. The RA was equal to the finally resected area, which had been determined based on the interictal and ictal EEG findings on intracranial video-EEG, MRI, and magnetoencephalography, as well as neuropsychological and neurological evaluations. The number of RA electrodes was 325.

2.4. MSE analysis

Electroencephalographic data were filtered using a 60-Hz notch filter and down-sampled to 200 Hz using the EEGLAB toolbox (http://sccn.ucsd.edu/eeglab). At the sampling rate of 200 Hz, the time scale factor $\tau = 3$ to 7 corresponded to the gamma frequency (28.6–66.7 Hz). We defined the MSE score for the entropy of GOs as the average MSE score with $\tau = 3$ to 7. We calculated the MSE score for each selected 20-s epoch. In this case, lower MSE scores represent lower entropy (higher regularity) of GOs. The detailed algorithm for

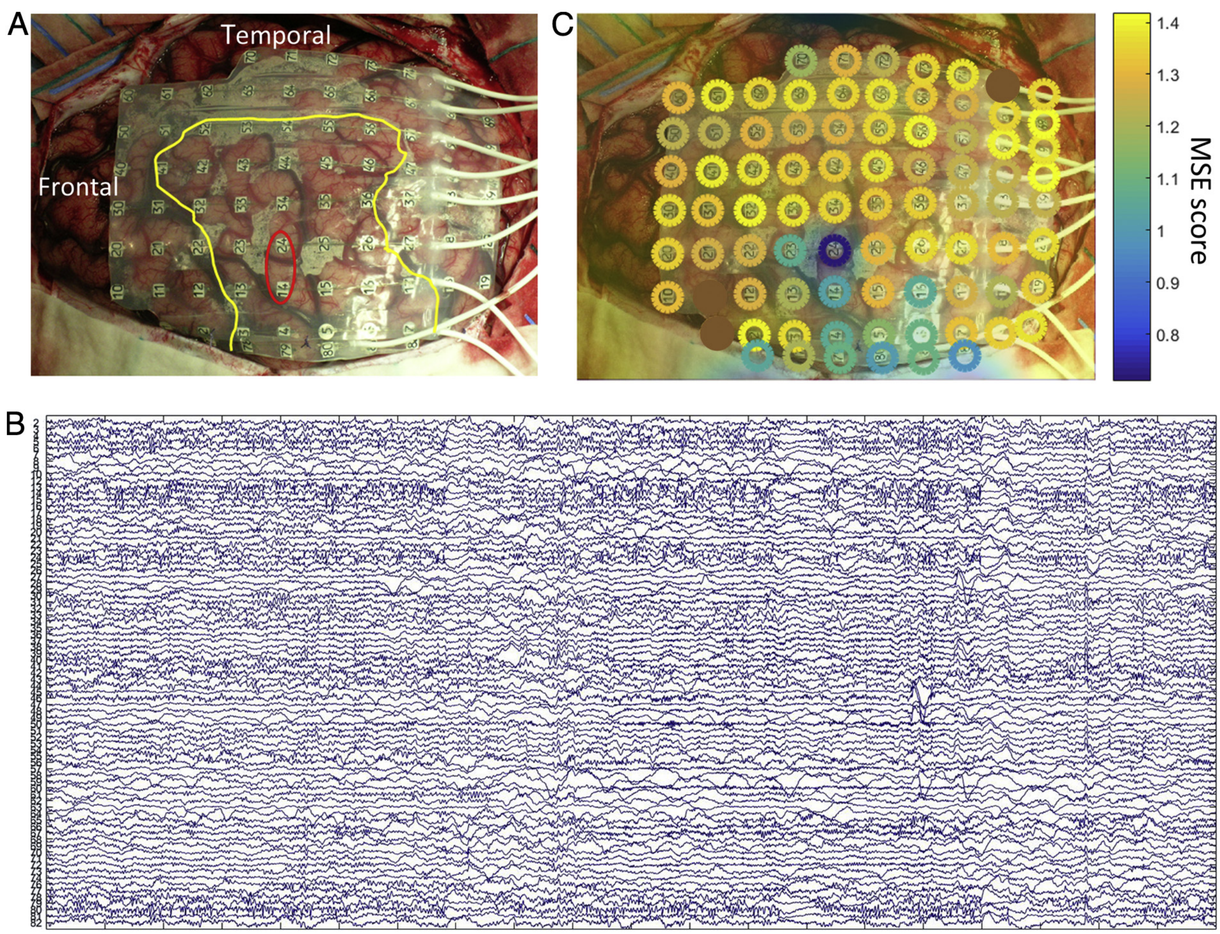


Fig. 1. Results in a representative case (right hemisphere). (A) The location of the seizure onset zone (SOZ; red circles, electrodes #14 and #24) and the resection area (RA; outlined in yellow) covered with the electrodes of subdural grid. Each electrode number corresponds to those in panels B and C. (B) Interictal 20-s epoch of EEG data filtered using a 60-Hz notch filter and down-sampled to 200 Hz, which was used for multiscale entropy (MSE) analysis. The electrode #1 was selected as a reference, and the electrodes #11 and #75 were excluded because of artifacts. (C) Color-coded MSE scores topographically superimposed onto the electrodes of the grid. #24 electrode shows the lowest MSE indicating the lowest entropy of interictal gamma oscillations corresponding with the SOZ.

this MSE analysis is described in our previous study [8]. The procedures were performed using a custom program written in MATLAB (The MathWorks, Version 8.5, Natick, MA, USA).

2.5. Statistical analysis

We calculated the mean and standard deviation (SD) of the measured MSE scores within a given patient. Z values were calculated using the following equation:

$$Z = ([\text{individual MSE score}] - [\text{mean MSE score}])/(\text{SD of MSE scores})$$

Calculations were performed for each individual electrode of each patient. Lower Z values represent higher regularity of GOs. To visually assess the Z value distribution, we created histograms wherein the cumulative numbers of electrodes were plotted against Z values across all patients for the SOZ, the RA, and the region outside the RA. We evaluated differences in Z values among the SOZ, the RA, and the region outside the RA using a one-way ANOVA and Scheffe's post hoc test. We used the area under the receiver operating characteristic (ROC) curve (AUC) to construct a graphic representation of the relationship between the sensitivity and specificity for the detection of the SOZ, the RA, and the region outside the RA. We then calculated the cutoff Z value, the sensitivity, and the specificity using ROC analysis. The statistical analyses were performed using MATLAB (The MathWorks, Version 8.5, Natick, MA, USA) and Microsoft Excel 2010 (Microsoft Corp., Seattle, WA, USA).

3. Results

3.1. Distribution of Z values

The MSE results in a representative case are shown in Fig. 1. The Z value histogram for all electrodes indicates that Z values were very low in the SOZ and relatively high in the RA and the region outside the RA (Fig. 2A). Data are presented as means ± SD. Z values in the SOZ (−3.54 ± 1.04) were significantly lower than those in the other two areas ($p < 0.001$, ANOVA, Scheffe's post hoc test). Z values in the RA (−0.53 ± 1.29) were significantly lower than those in the region outside the RA (0.21 ± 0.77) ($p < 0.001$; Fig. 2B).

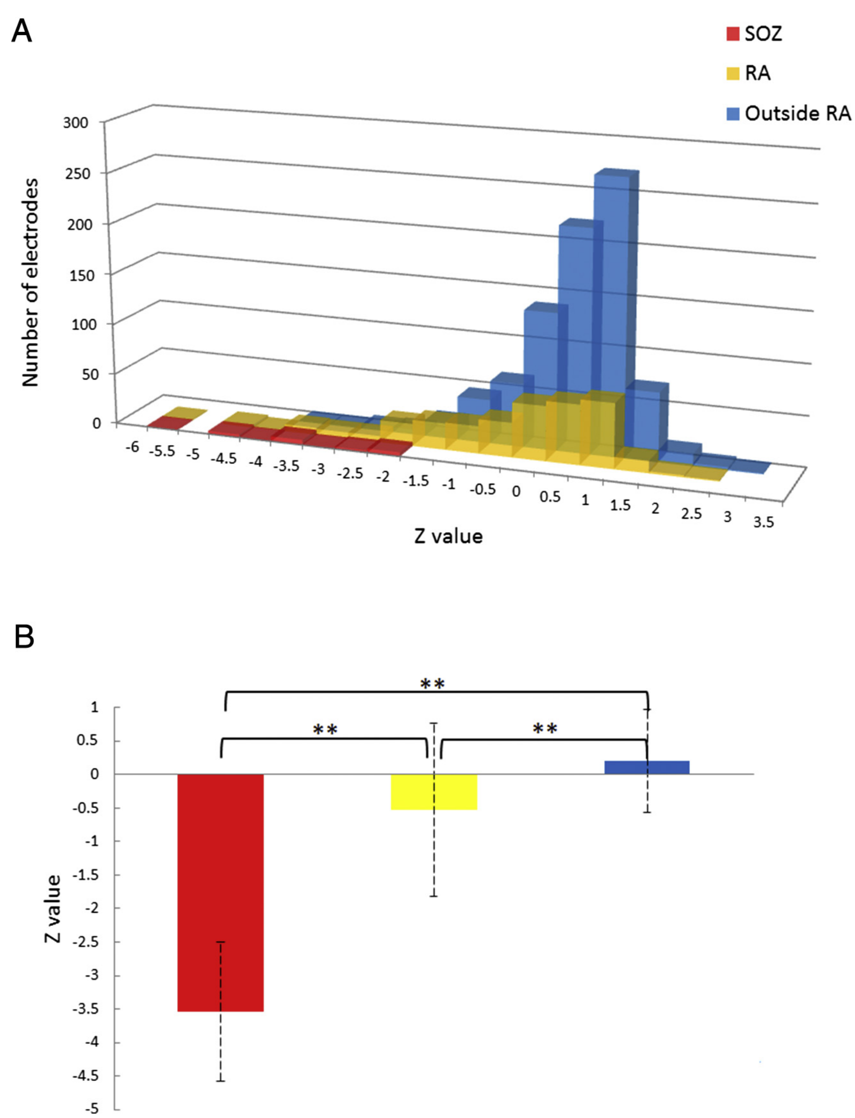
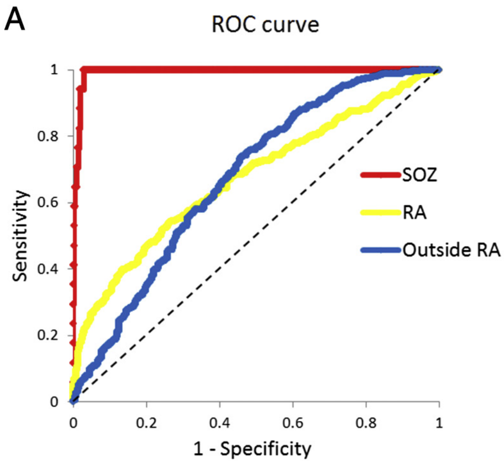


Fig. 2. (A) Distributions of Z values across all patients by area. Red: seizure onset zone (SOZ); yellow: resection area (RA); and blue: region outside the RA. (B) Comparison of Z values among the SOZ, the RA, and the region outside the RA using a one-way analysis of variance and Scheffe's post hoc test (** $p < 0.01$). Bars indicate standard deviation.



B

Cutoff Z value, sensitivity, and specificity for detection of the SOZ, the RA, and outside RA

	Cutoff Z value	Sensitivity (%)	Specificity(%)	AUC ± SEM
SOZ	-2.09	100	97.1	0.992 ± 0.002
RA	-0.12	54.2	73.8	0.673 ± 0.019
Outside RA	-0.11	73.8	54.2	0.673 ± 0.019

Fig. 3. Results of the receiver operating characteristic (ROC) curve analysis. (A) The ROC curves for detection of the seizure onset zone (SOZ), the resection area (RA), and the region outside the RA based on quantification of the regularity of interictal gamma oscillations. (B) Cutoff Z values, sensitivity, and specificity for the detection of the SOZ, the RA, and the region outside the RA. AUC, area under the ROC curve; SEM, standard error of the mean.

3.2. Sensitivity and specificity for the detection of the SOZ, the RA, and the region outside the RA

There were 17 electrodes in the SOZ and 325 electrodes in the RA. The ROC curve, cutoff Z value, sensitivity, specificity, and AUC values are summarized in Fig. 3. For the detection of the SOZ, Z values ≤ −2.09 had a sensitivity of 100% and specificity of 97.1% (AUC = 0.992 ± 0.002); for the RA, Z values ≤ −0.12 had a sensitivity of 54.2% and specificity of 73.8% (AUC = 0.673 ± 0.019); and for the region outside the RA, Z values ≥ −0.11 had a sensitivity of 73.8% and specificity of 54.2% (AUC = 0.673 ± 0.019). Since the whole analysis area was just divided into the RA and the region outside the RA, the sensitivity and specificity reversed their values to each other, and AUC +/− SEM values were exactly the same values.

4. Discussion

The low entropy of interictal GOs (low Z values) was reliable biomarkers for the SOZ in a subset of patients with neocortical FCD type II. Local interneuron activity is associated with the rhythmic synchronization of GOs [5]. Specifically, synchronous gamma-butyric acid A receptor-dependent activity plays a pivotal role in the focal ictogenesis observed in neuronal networks in FCD [9,10]. Our previous study showed that altered network synchronization, including altered GOs, is intimately involved in seizure initiation and propagation [11]. Another study has also reported that seizures are caused by the breakdown of the inhibitory synchronous system that isolates the SOZ from the surrounding epileptogenic zone [12]. We speculate that inhibitory interneuron synchronization in the SOZ is expressed as very low Z values during interictal periods. Based on these pathophysiological mechanisms, the lowest entropy (highest regularity) of interictal GOs (lowest Z values) may be a biomarker for the SOZ on intracranial EEGs in patients with FCD type II (Table 1).

Maintained high entropy of interictal GOs (high Z values) may be related to an auxiliary biomarker of the area outside the epileptogenic zone. Interneuronal activities that are coherent with GOs do not exhibit increased synchrony until spontaneous seizure occurrence [13]. The hypersynchronous recruitment of both inhibitory and excitatory interneuronal networks does not occur before a seizure [1]. The irregularity of interictal GOs was consistent (high Z values) outside the RA, which is a nonepileptogenic region, during the interictal, preictal, and ictal periods in our previous study [8]. The nonepileptogenic normal network outside the FCD type II does not participate in the epileptic network, even during seizures. The RA in this study could cover the epileptogenic zone because of seizure-free outcome. The individual electrode analysis of the entropy of interictal GOs may accurately differentiate the epileptogenic lesion from nonepileptogenic areas (Table 1).

There is a possibility of physiological high entropy or low entropy of GOs at some cortical sites. Nagasawa et al. demonstrated that nonepileptic occipital lobes show high-gamma activity periodically at 0.5–1 Hz during slow-wave sleep [14]. Normative data would be useful to further validate the utility of our MSE analysis in presurgical evaluation.

Table 1
Relationship between entropy, regularity of interictal GOs, and detection site.

Entropy	Regularity of interictal GOs	Detection site
Low	Regular	SOZ
High	Irregular	Nonepileptogenic lesion

GOs, gamma oscillations; SOZ, seizure onset zone.

There are limitations to this study. First, the interictal EEG data were diverse. We randomly selected three interictal segments during non-REM sleep and confirmed that there were no significant differences among MSE score variances ($p > 0.05$) and MSE scores ($p > 0.05$) using Bartlett's test and a one-way ANOVA. Second, very few electrodes were defined as the SOZ (total of 17 contacts in 13 patients) in this study. We selected SOZ as the electrodes where low amplitude HFO started. In the cases with intrinsically focal epileptogenic FCD type II, the focal onset seizures often started at the discrete area. This is because only one seizure per patient was used to determine the SOZ and the subjects were limited to FCD type II that is intrinsically and focally epileptogenic [15]. Further studies will be needed to explore the spatiotemporal distribution of EEG regularity in each frequency band using MSE for other types of brain lesions.

In FCD type II, the low entropy of interictal GOs (low Z values) obtained from intracranial EEG was found to be a biomarker for the SOZ, while maintained high entropy of interictal GOs (high Z values) may be an auxiliary biomarker for the nonepileptogenic region.

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