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Discrete gamma oscillations identify the seizure onset zone in some pediatric epilepsy patients

Jay R. Gupta*, Eric D. Marsh*, Horng-An Edward Nieh, Brenda E. Porter, and Brian Litt

Abstract—**Intracranial electroencephalography (IEEG) plays an important role in guiding epilepsy surgery in pediatric epilepsy patients. Recently, there has been increased interest in higher frequency components of clinical IEEG recordings and their potential relationship to epileptogenic brain tissue. We employ a previously validated, automated discrete gamma oscillation (GO) detection algorithm to determine the prevalence of discrete gamma events over prolonged, representative segments of IEEG recorded from ten patients. Approximately 8 h of IEEG, 16 randomly selected 30-min segments of continuous interictal IEEG per patient, were analyzed. The electrodes within the seizure onset zone were found to have significantly higher mean GO activity averaged across these 16 segments in five of the ten patients. There was observed variability between individual 30-min segments in these patients, indicating that longer recordings of interictal activity improved localization. Our data suggest this method of automated GO detection across long periods may be useful in planning epilepsy surgery in certain children with intractable epilepsy. Further research is required to help determine which patients would benefit from this technique.**

I. Introduction

SURGERY is a well-established treatment for patients with medically refractory epilepsy and evidence of seizure onset arising from a localized or regional zone. Intracranial electroencephalogram (IEEG) recordings are often used to help define seizure onset zone and potential targets for resection, especially in patients with extratemporal epilepsy. However, intracranial electrode implantations do not always improve localization and potentially increase the morbidity of the procedure. For this reason, additional methods to improve presurgical localization of the seizure onset zone are needed. This study analyzes the occurrence of discrete gamma oscillations (GOs) over extensive amounts of clinical IEEG recordings from pediatric epilepsy patients to determine if a quantitative analysis of GOs can improve localization of the seizure onset zone.

Recent studies of IEEG recordings have described high frequency activity in normal brain functions such as learning and memory consolidation (~ 40 – 200 Hz) [1], [2] as well as an increase in activity leading up to seizure onset [3], [4]. These studies, among others, are part of an increasing interest within the epilepsy research community in the possibility that the presence of discrete high frequency activity could be used to identify epileptogenic brain tissue. Further studies are still needed to help determine the potentially various quantitative relationships between such high frequency waveforms and seizure onset. To our knowledge, this study, which examines 8 hours of IEEG per patient representative of recordings taken over several days, is the first report to analyze the relationship between high frequency activity and seizure onset zone over long periods of recording.

Historically, many human studies that use presurgical IEEG recordings for evaluation of patients with intractable epilepsy report a limited frequency range (~ 0.1 – 30 Hz) of activity [5], [6]. This may be due to the fact that higher frequency oscillations have relatively smaller amplitudes and can be easily obscured by lower frequency activity. We hypothesize that there is significant information to be extracted from the frequency range above 30 Hz that could be used to improve localization of seizure onset. We have attempted to map the occurrence of GOs in long-term IEEG recordings in a group of children with intractable epilepsy, with the goal of determining if the location of frequent GOs is a surrogate marker for seizure onset.

II. Methods[1]

A. Clinical data

The Children's Hospital of Philadelphia (CHOP) Institutional Review Board approved this study. IEEG recordings were obtained prospectively from 30 patients undergoing subdural electrode implantation for epilepsy surgery between 2003 and 2007. All IEEGs were recorded with Grass-Telefactor 128 Electrode CTE EEG machine

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*J. R. Gupta and E. D. Marsh contributed equally to this work.

J. R. Gupta is with the Departments of Neurology and Bioengineering, The University of Pennsylvania, Philadelphia, PA 19104 USA (phone: 215-573-8392; fax: 215-573-8393; e-mail: jaygupta@seas.upenn.edu).

E. D. Marsh and B. E. Porter are with the Division of Child Neurology, Department of Neurology and Pediatrics, Children's Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, PA 19104 USA (e-mail: marshe@email.chop.edu; porterb@email.chop.edu).

H.E. Nieh and B. Litt are with the Departments of Neurology and Bioengineering, The University of Pennsylvania, Philadelphia, PA 19104 USA (e-mail: enieh@seas.upenn.edu; littb@mail.med.upenn.edu).

[1] Since there is significant overlap between the patients used in this study and the patients used in a previous study done by our group [7] all methods related to clinical data as well as patient/segment data is similar.

using 16-bit amplifiers (Astro Med Corp., West Warwick, RI, U.S.A.) sampled at 200 samples/s/electrode. Analog antialiasing bandpass filter (frequency cut-offs at 0.1 Hz and 70 Hz) and notch filter (null at 60 Hz) were used for signal conditioning. Recordings were reviewed in a referential montage and marked by two reviewers to identify seizure onset times, morphology, and electrode locations.

B. Patient selection

From 30 consecutively consented patients, 10 patient's IEEGs were selected for the current study. Patients were chosen using the following criteria: detailed IEEG seizure markings were present, recordings were continuous and predominantly artifact free, and interictal epileptiform activity was present.

C. Seizure onset determination

Two clinical epileptologists marked seizure onset times and locations. Clinical reports were consulted, but the entire recording was reviewed for the presence of seizures. All electrographic seizures were marked for times of unequivocal seizure onset and earliest electrical change [8]. Final consensus between the two IEEG readers established which electrodes were involved at seizure onset and the exact onset times for each seizure. All electrodes determined to be involved at the unequivocal electrographic onset were included in the seizure onset zone calculations.

D. GO detection

An automated detector was implemented in MATLAB (Natick, MA, U.S.A.) that was adapted from a previously validated automated high-frequency oscillation (HFO) detector described previously by our group [9]. Table I summarizes the key parameter values used in the detector (A) as well as the key parameter values used in the previously validated detector (B).

Briefly, this method for identifying GOs models the events as short-duration, high-frequency oscillatory transients. Events are identified by first bandpass-filtering the EEG data using MATLAB's filtfilt function to restrict the range of frequencies under consideration. Detection then consists of taking a running measure of the short-time energy and applying a threshold. In this case, post-detection filtering methods including event duration threshold and ripple counting were used to further confirm detections.

TABLE I
SUMMARY OF AUTOMATED DETECTOR CHARACTERISTICS

Characteristic	A	B
Data Bandwidth	0.1 – 100 Hz	0.1 – 100 Hz
Bandpass Filtering	30 – 85 Hz 4th order Butterworth	30 – 85 Hz 4th order Butterworth
Energy Measure	RMS amplitude	RMS amplitude
Energy Measure Window Size	50 ms (10 samples)	85 ms (17 samples)
Threshold	$\mu + 0.9\sigma$ (global)	$\mu + 2.5\sigma$ (global)
Minimum Event Duration	6 ms	80 ms
Ripple Count Criteria	8-peak minimum	None

For this study the detector was "tuned" for this particular group of patients. The detector's output was plotted against the IEEG of several representative patients and reviewed by an epileptologist to determine the validity of the detections. We wished to attain the lowest number of false positive detections as well as highest number of true positive detections. The reviewer had to qualitatively agree with the HFO detections or the detector thresholds were recalculated.

E. Segment selection

The full duration of each patient's IEEG recording was divided into 30-min segments. A MATLAB random number algorithm reordered the segments, with the first 16 being reviewed. If the randomly chosen segment contained a seizure or was interrupted by file change, the next segment in the list was used. After the original segment selection was completed, one segment, determined to be unusable due to artifacts, was discarded. This resulted in one patient having only 15, 30-min segments for analysis.

F. Statistical analysis

The selected segments were analyzed using the predetermined thresholds and the output sorted by electrode and segment. The mean GO density (GOs/30 min/electrode) was calculated for each patient. For each patient, the location of each electrode was extracted from surgical photographs, schematic drawings, and postimplant magnetic resonance imaging (MRI), when available. This information was used to plot the mean GO densities on X-Y coordinate plots of the electrode grids. This process is illustrated in Fig. 1.

Quantitative assessment was performed using a Mann-Whitney *U* test to compare mean GO counts across all 30-min segments in channels within or outside the seizure onset zone. All calculations were performed in MATLAB using the statistical toolbox. Our original question was to determine if GO density could identify seizure onset electrodes. Our null hypothesis was no difference in mean GO count between seizure onset and other electrodes existed. These tests were two-sided and a significance level of 0.05 was used.

Since we found a mixture of patients with and without GO density correlation to seizure onset we further explored intraptient segmental variation by performing another Mann-Whitney *U* test to compare the GO counts in each 30-min segment in channels within or outside the seizure onset zone. This tested for variability of seizure onset with GO density across segments for a single patient.

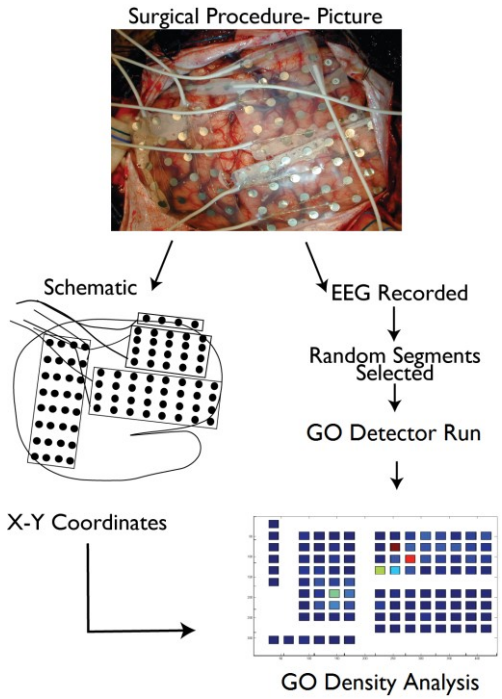

Fig. 1. Procedure for plotting the mean GO density as it relates to electrode location/spacing as well as seizure onset vs. all other electrodes. The spatial information about the electrode grids is obtained from pictures taken at the time of implantation. This information is transformed to the X-Y plane. The GO detector is run and a color-coded map of HFO density is created (red = more GOs, blue = fewer GOs). Seizure onset electrodes are denoted by a solid black border.

III. Results

Mean GO densities (GOs/30 min/electrode) across all processed data epochs for each patient were compared to that patient's seizure onset zone. A Mann-Whitney *U* test was calculated to quantify the relationship between GO density and seizure onset. Five of the ten patients (50%) had mean GO densities in seizure onset channels that were significantly different from the mean GO densities in all other channels ($p < 0.05$; Table II).

We also assessed if GO density correlation with seizure onset channels remained constant across all segments for each patient. The Mann-Whitney *U* test revealed that in the five patients described earlier with significant correlation between mean GO density and seizure onset zone, up to 11 (range 3-11) of the *p*-values of the 16 individual segments was >0.05. For the five patients whose 16-segment average showed no significant correlation ($p > 0.05$) there was also variability between segments, with zero to three segments having significant correlation ($p < 0.05$) between GO density and seizure onset zone. Only two of the ten patients demonstrated no variation of significance across all 16 30-min segments. Overall, 32.08% of the 159 IEEG segments analyzed had GO densities that correlated with seizure onset zones. This is a considerable difference from the 50% of patients that exhibited a correlation, therefore increased data sampling/averaging significantly improves the likelihood that GO distribution correlates with seizure onset zone.

TABLE II
Statistical Analysis of Mean GO Density Versus Seizure Onset Zone

Patient no.	*p*-value	No. significant segments ($p<0.05$)
1	0.1614	3
2	*0.0082*	*11*
3	0.4273	2
4	0.5451	0
5	*0.0275*	*5*
6	*0.0003*	*10*
7	*0.0391*	*13*
8	0.1517	0
9	0.0630	1
10	*0.0038*	*6*

IV. Discussion

Implementation of a computerized, automated GO detection algorithm allowed us to analyze extremely long periods of IEEG. Using the resulting detection information, we were able to identify a correlation between the locations of interictal GO prevalence and the seizure onset zone in five of ten patients. In the other five patients, GO density was not a good marker for identifying the seizure onset zone. In addition, we found that GO density varied significantly between different 30-min segments of IEEG recorded from the same patient. Only two of the patients demonstrated no variation of correlation across segments. These results support the idea that brief recordings of GOs are unlikely to be useful in localizing seizure onset.

Significant proliferation of high-frequency oscillations within the seizure onset zone in the 20 minutes prior to seizure onset has been documented in adult patients with epilepsy [3]. Although our analysis did not make an attempt to focus on only the period immediately prior to seizure onset, the sparseness of our segments selected for analysis as well as the variability in correlation across segments within each patient implies that the time picked to quantify GO density likely affects how well this measure could help define the seizure onset zone.

Although these findings support a correlation between GO density and seizure onset zone in some patients, the current results do not support using only GO density as a predictive model in order to determine seizure onset zone. Even in the cases where a correlation between GO density and seizure onset zone is observed, by inspection of Fig. 2 it should be clear that there are channels with high levels of detected GOs that fall outside the seizure onset zone as well as channels with low levels of GOs that fall within the seizure onset zone. Further studies are necessary in order to explore the relationship between seizure onset zone, the brain tissue that was ultimately resected, patient outcome, the pathology of the concerned tissue areas, and how GO density varied in all of these areas.

One interesting finding is that the discrete gamma oscillatory events detected in this study differ from the

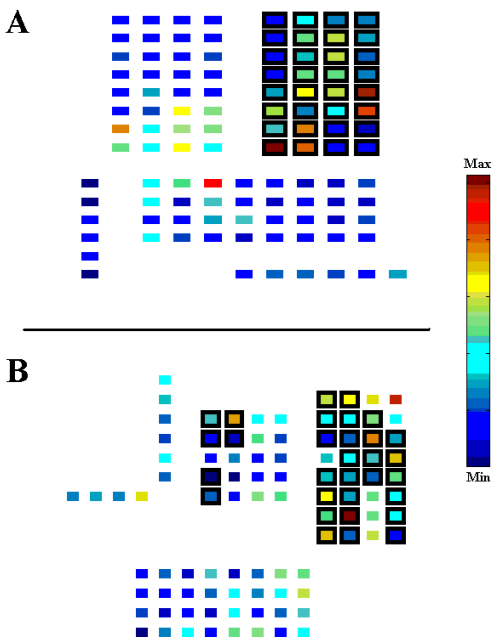

Fig. 2. Two patients (A=Patient 6, B=Patient 7) demonstrating strong correlation of GO density with seizure onset electrodes. These are electrode maps demonstrating areas of high mean GO density, averaged across all segments for each patient, as red and areas of low GO density as blue. Seizure onset electrodes are identified by a dark outline. Some electrodes with high GO density remain outside the seizure onset region in both patients.

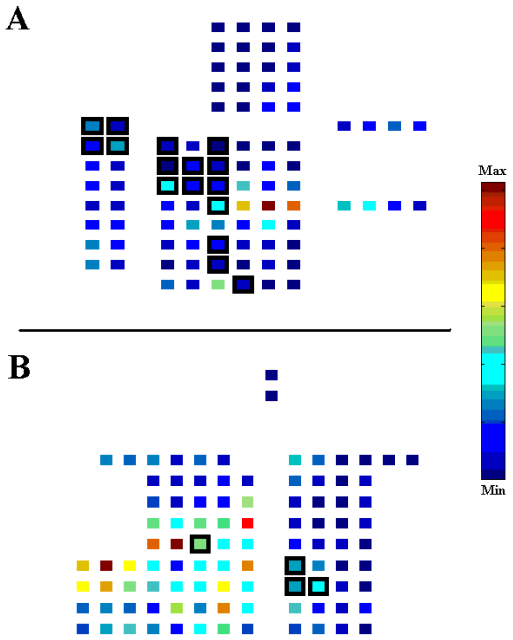

Fig. 3. Two patients (A=Patient 8, B=Patient 1) demonstrating a lack of correlation of GO density with seizure onset electrodes. These are electrode maps demonstrating areas of high mean GO density, averaged across all segments for each patient, as red and areas of low GO density as blue. Seizure onset electrodes are identified by a dark outline. Some electrodes with moderate GO density lie within the seizure onset region in both patients.

higher frequency, 100-500 Hz, oscillations associated with mesial temporal and non-lesional neocortical epilepsies [3], [10]. Data in the present study were acquired at sampling rates too low, 200 Hz post antialias filtering, to adequately capture the previously mentioned higher frequency oscillations. Patients in the current study are children primarily with visible cortical dysplastic lesions, a group that is not well represented in this literature.

V. Conclusion

In this study we used an automated algorithm to detect and quantify discrete gamma oscillations over long periods of IEEG. Using these detections we were to able identify patients with and without a correlation between GO density and seizure onset zone. Although our results indicate a relationship between GO prevalence and epileptogenic brain tissue, there still remain many open questions about the details and specifics of this relationship. It will also be important to determine how this relationship can be used to help define seizure onset zone. At present, a major concern is the difficulty of determining a method by which seizure onset channels are selected based solely upon automated detections of high frequency waveforms.

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