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High kurtosis of intracranial electroencephalogram as a marker of ictogenicity in pediatric epilepsy surgery

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HIGHLIGHTS

- Kurtosis analysis of intracranial electroencephalogram is helpful to predict post-surgical seizure outcome in pediatric epilepsy surgery.
- The brain regions with high kurtosis provide more reliable information to predict seizure outcome than the seizure onset zone and the regions with high-rate/amplitude and long-duration interictal paroxysms $\geqslant$20 Hz.
- Kurtosis reflects combined effects of the amplitude and duration of interictal paroxysms.

ABSTRACT

Objective: We determined whether kurtosis analysis of intracranial electroencephalogram (EEG) can estimate the localization of the epileptogenic zone.
Methods: We analyzed 29 pediatric epilepsy patients who underwent intracranial EEG before focal resective surgery. We localized the brain regions with high kurtosis, the seizure onset zone (SOZ) and the regions with high-rate, high-amplitude and long-duration interictal paroxysms $\geqslant$20 Hz. We tested correlations between the surgical resection of those regions and post-surgical seizure outcome, and correlations between kurtosis and the rate/amplitude/duration of interictal paroxysms.
Results: The resection of the regions with high kurtosis correlated with 1-year post-surgical seizure outcome ($p = 0.028$) but not with 2-year outcome. Kurtosis showed more significant correlation with 1-year seizure outcome than the SOZ and the rate/amplitude/duration of interictal paroxysms. Kurtosis showed positive, independent correlations with the amplitude and duration of interictal paroxysms ($p < 0.0001$) but not with the rate ($p = 0.4$).
Conclusions: The regions with high kurtosis provide more reliable information to predict seizure outcome than the SOZ and the regions with high-rate/amplitude and long-duration interictal paroxysms. Kurtosis reflects combined effects of the amplitude and duration of the interictal paroxysms.
Significance: High kurtosis suggests the regions with acquired ictogenicity within the irritative zone.

1. Introduction

Kurtosis, from the Greek word “kurtos” meaning “bulging” or “swelling”, is a measure of the “peakedness” or “spikiness” of a distribution in statistics. A distribution with high kurtosis generally has a distinct peak around the mean, rapid declines but heavy tails. Outliers make the tails heavy and increase kurtosis; therefore, kurtosis is used as a measure of presence of outliers (Livesey, 2007). In epilepsy patients, the occurrence rate, amplitude and duration of spikes on electroencephalogram (EEG) probably correlate with the number of outliers in EEG voltage data, because spikes are in higher amplitude than the background activity. EEG signals with frequent interictal spikes can have high kurtosis values due to presence of many outliers.

Kurtosis analysis was initially applied to interictal magnetoencephalography (MEG) studies in epilepsy patients (Robinson et al., 2004). The brain region with high-kurtosis magnetic activities correlated with the localization of clustered equivalent current dipoles for interictal MEG spikes, which correlated with the epileptogenic zone (Fischer et al., 2005; Iida et al., 2005a,b; Kirsch et al., 2006; Oishi et al., 2006; Mohamed et al., 2007; RamachandranNair

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et al., 2007; Sugiyama et al., 2009). Kurtosis analysis has never been applied to intracranial EEG which could directly record epileptic discharges from the brain surface and within the cortex.

In designing strategies for the resective epilepsy surgery, different zones have been proposed to explain how the epileptic network generates seizures. The epileptic network consists of four zones: seizure onset zone (SOZ), symptomatogenic zone, irritative zone and epileptogenic zone, with and without epileptogenic lesion (Rosenow and Lüders, 2001). Theoretically, complete surgical resection of the epileptogenic zone is necessary and sufficient to achieve a seizure free outcome.

This is the first study of kurtosis analysis applied to the intracranial EEG. We evaluated whether kurtosis analysis was valuable for the intracranial EEG data to localize the epileptogenic zone, comparing with seizure outcomes and the SOZ. We also investigated the relationship of kurtosis with three characteristics of interictal paroxysms (occurrence rate, amplitude and duration) to see what neurophysiological characteristics kurtosis reflected. We hypothesized that (1) resection of the brain regions with high-kurtosis EEG activities would result in better seizure outcome, (2) kurtosis would be more correlated with seizure outcome than the SOZ, rate/amplitude/duration of interictal paroxysms, and (3) kurtosis would show positive correlations with rate/amplitude/duration of interictal paroxysms.

2. Methods

2.1. Subjects

We retrospectively included 29 pediatric patients ($\leqslant$18 year of age) who underwent intracranial video EEG (VEEG) monitoring to localize seizure onset and delineate the extent of the presumed epileptogenic zone prior to focal resective surgery between July 2004 and June 2008. This study was approved by the Research Ethics Board at the Hospital for Sick Children.

2.2. Intracranial VEEG

The technique of implantation of intracranial electrodes, mapping of the possible epileptogenic zone, and intraoperative and extraoperative functional mapping of eloquent cortex was done as described previously (Benifla et al., 2009; Pang et al., 2009). Center to center spacing of the contacts ranged from 6.5 to 10.5 mm in subdural electrodes and was 7 mm in depth electrodes (Ad-Tech medical instrument, Racine, WI, USA). Intracranial VEEG was recorded using the Harmonie system (Stellate, Montreal, PQ, Canada) with two electrodes over the brain regions without active epileptiform discharges used as linked references. The EEG signals were sampled at 1 kHz after band-pass filtering at 0.016–300 Hz.

2.3. Resective surgery and seizure outcome

The resection margin was determined based on the visual and spectral analyses (Ochi et al., 2007) of ictal intracranial VEEG, interictal epileptiform discharges on intracranial VEEG, equivalent current dipoles for the interictal epileptiform discharges on MEG, and location of eloquent cortices revealed by functional mapping using direct cortical stimulation and sensory evoked potentials. The SOZ was determined by clinical neurophysiologists by visual and spectral analyses of ictal intracranial VEEG. Because this is a retrospective study, the surgical decision was not based on the results of this study. This fact is advantageous to optimize outcome prediction, as we can compare outcome in the patients where high-kurtosis regions were resected with those where high-kurtosis regions were not.

We determined postsurgical seizure outcomes at 1 and 2 years according to the ILAE classification (Wieser et al., 2001). For statistical analyses, we simplified the seizure outcome into two groups based on the seizure burden during the 1 year/2 years following surgery: (1) seizure free, completely seizure free without auras following surgery; (2) not seizure free.

2.4. EEG data selection

We selected 10 epochs of 2-min interictal EEG during sleep for each subject so that they were remote from each other and from seizures by at least 1 h. We selected EEG epochs with increased slow waves while the patient was asleep. We chose to select multiple epochs rather than analyzing a long epoch (e.g. 20-min EEG) to reflect the variability of interictal paroxysms over days as much as possible. Each selected epoch was visually inspected to ensure it was not contaminated by significant artifacts, such as environmental artifacts and muscle artifacts (Otsubo et al., 2008).

2.5. Calculation of kurtosis

The EEG data were analyzed in the referential montage using a common average reference to eliminate contamination from the recording references. The analysis was done by a custom-made program written in MATLAB (The MathWorks, Natick, MA, USA). We analyzed all the channels except for those used as recording references and those with poor contact.

Before computing kurtosis, we filtered the EEG signal by a high-pass filter at 20 Hz (4th-order Butterworth, bidirectional filtering) to enhance interictal paroxysms. This cut-off frequency was selected based on the past MEG study on kurtosis reported by Robinson et al. (2004). The kurtosis (more strictly "excess kurtosis") for the filtered EEG signal from each channel is calculated as:

$$\text{Kurtosis} = \left[\sum_{k=1}^{N}(x_k - \mu)^4/(N\sigma^4)\right] - 3$$

where x_k ($k = 1, 2, \ldots N$) is the time samples of the filtered EEG, μ is the mean and σ is the standard deviation of x_k. With this definition, a Gaussian signal has a kurtosis of zero.

2.6. Calculation of the rate, duration and amplitude of interictal paroxysms

Using the same EEG data high-pass filtered at 20 Hz, we detected interictal paroxysms by the following method. The algorithm of this analysis is analogous to the automated detection of high-frequency oscillations described elsewhere (Staba et al., 2002; Gardner et al., 2007; Schevon et al., 2009; Crépon et al., 2010). First, we performed Hilbert transform for the EEG to obtain the EEG signal envelope curve. Interictal paroxysms appear on the envelope curve as intermittent peaks that clearly stand out from the background epochs (outliers). Second, from the distribution of the envelope curve value, we set the cut-off line to detect these outliers. For this purpose, we used Tukey's upper outer fence (Tukey, 1977), which is calculated by 75th percentile value +3 × interquartile range (IQR). Any values exceeding this cut-off line were considered to be outliers. Third, when outliers appeared in consecutive time points lasting $\geqslant$20 ms, the epoch with these outliers was declared to be an interictal paroxysm. This duration criterion was chosen since spikes on EEG generally last $\geqslant$20 ms. From the detected interictal paroxysms, we calculated the rate (/min), mean amplitude and mean duration of the paroxysms in each channel. When the rate was zero, mean amplitude and duration were treated as missing values.