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Seizure prediction in patients with focal hippocampal epilepsy

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HIGHLIGHTS

- Our rule-based seizure prediction system provided an average sensitivity of >90%.
- Nonlinear analysis revealed patient-specific changes prior to hippocampal seizures.
- Preictal changes in iEEG data occurred in epileptogenic zones and remote areas.

ABSTRACT

Objective: We evaluated the performance of our previously developed seizure prediction approach on thirty eight seizures from ten patients with focal hippocampal epilepsy.
Methods: The seizure prediction system was developed based on the extraction of correlation dimension, correlation entropy, noise level, Lempel-Ziv complexity, largest Lyapunov exponent, and nonlinear interdependence from segments of intracranial EEG.
Results: Our results showed an average sensitivity of 86.7% and 92.9%, an average false prediction rate of 0.126 and 0.096/h, and an average minimum prediction time of 14.3 and 33.3 min, respectively, using seizure occurrence periods of 30 and 50 min and a seizure prediction horizon of 10 s. Two-third of the analyzed seizures showed significantly increased complexity in periods prior to the seizures in comparison with baseline.
In four patients, strong bidirectional connectivities between epileptic contacts and the surrounding areas were observed. However, in five patients, unidirectional functional connectivities in preictal periods were observed from remote areas to epileptogenic zones.
Conclusions: Overall, preictal periods in patients with focal hippocampal epilepsy were characterized with patient-specific changes in univariate and bivariate nonlinear measures.
Significance: The spatio-temporal characterization of preictal periods may help to better understand the mechanism underlying seizure generation in patients with focal hippocampal epilepsy.

1. Introduction

Epilepsy is a neurological disorder affecting 1% of the world's population. It causes seizures characterized by recurrent synchronous abnormal electrical discharges in the brain (Chaovalitwongse et al., 2006; Browne and Holmes, 2008). Epileptic patients are often at high risk of serious injury or death (Cockerell et al., 1994). Moreover, accompanying psychological stress and helplessness can cause impaired everyday functioning (Buck et al., 1997; Baker et al., 1997). Thereby, reliable prediction of seizures can considerably improve the quality of life of epileptic patients by warning them of impeding seizures to avoid potentially dangerous situations like driving or swimming and enable administration of treatments (Cook et al., 2013; Ramgopal et al., 2014).

To date, linear and nonlinear analysis techniques have been applied in order to identify preictal periods by investigating various properties of the electroencephalography (EEG) signal, with varying degrees of success (see Litt and Echauz, 2002; Iasemidis, 2003; Mormann et al., 2006, 2007; Gadhoumi et al., 2016 for a review). A number of studies have employed univariate measures taken from the nonlinear dynamics chaos theory, including the

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Table 1
Patients and intracranial EEG data characteristics.

Patient	Sex	Age	Seizure type	Origin	Electrodes	# seizures		Interictal EEG duration (h)	
						Training set	Testing set	Training set	Testing set
1	M	38	SP,CP,GTC	Temporal	d	1	2	4	20
2	F	26	SP,CP,GTC	Temporal	d,g,s	1	4	4	20
3	F	31	CP,GTC	Temporo/Occipital	d,g,s	1	2	4	20
4	F	42	SP,CP,GTC	Temporal	d	1	2	4	20.6
5	M	47	SP,CP,GTC	Temporal	d	1	4	4	20.5
6	F	42	SP,CP,GTC	Temporal	d,g,s	1	3	4	21
7	F	22	SP,CP,GTC	Temporo/Occipital	d,s	1	1	4	20
8	F	41	CP,GTC	Fronto/Temporal	d,s	1	3	4	20
9	M	31	SP,CP,GTC	Temporal	d,s	1	3	4	20
10	F	50	SP,CP,GTC	Temporal	d,s	1	4	4	20
Total	7F/3M					10	28	40	202
Mean							3		20

SP = simple partial, CP = complex partial, GTC = generalized tonic-clonic, g: grid, s:strip, d:depth

correlation dimension (Lehnertz and Elger, 1995; Lehnertz et al., 2001), correlation density (Martinerie et al., 1998), largest Lyapunov exponent (Iasemidis et al., 1990), dynamic similarity index (Le Van Quyen et al., 2001), entropy (Van Drongelen et al., 2003) and predictability (Drury et al., 2003). Nonlinear EEG analysis using univariate measures has provided evidence that transitions between interictal and ictal states may begin from minutes to hours prior to seizures, with characteristic changes evolving from a high complexity (possibly chaotic) to a low complexity (rhythmic behavior during a seizure) (Basar, 1998).

Based on the hypothesis that interactions between different neuronal networks involved in the epileptogenic process may also change prior to the seizure onset, many researchers have employed bivariate measures, such as nonlinear interdependence (Arnhold et al., 1999), phase synchronization, and cross correlation (Mormann et al., 2000, 2003) to predict seizures.

In our previous study, we developed a patient-specific method with significantly improved performance to predict partial seizures in patients with focal neocortical epilepsy using intracranial EEG (iEEG) data by combining the univariate and bivariate nonlinear measures (Aarabi and He, 2012). In the present study, we employed the same seizure prediction system to iEEG data of patients with medically intractable focal hippocampal epilepsy. The dynamic characteristics of the iEEG were extracted and spatiotemporally integrated using patient-specific rules established based on a template seizure from each patient. We evaluated the performance of the individual univariate and bivariate measures as well as the combination method for seizure prediction. Finally, the dynamic of the preictal states associated with focal hippocampal seizures was compared with that we previously reported in patients with focal neocortical epilepsy (Aarabi and He, 2012).

2. Methods

2.1. EEG data

The iEEG data analyzed in this study were obtained from the Freiburg Seizure Prediction EEG (FSPEEG) database collected from 21 patients with medically intractable focal neocortical and hippocampal epilepsy (Maiwald et al., 2004). We already used the iEEG data of 11 patients with neocortical focal epilepsy to evaluate the performance of our seizure prediction method (Aarabi and He, 2012). In the present paper, we evaluated the same system with the remaining iEEG recordings of 10 patients with seizures initiated in the hippocampus, which is known as a region more susceptible to make abrupt transitions to seizures (Sackellares et al., 2000). To record the iEEG data, patients had been implanted with intracranial electrodes, from which three within the epileptogenic zone and three in remote locations had been selected by an experienced epileptologist and included in the FSPEEG database. In total, 280 h of iEEG data containing 38 seizures with at least 50 min preictal data and 24-h seizure-free interictal data for each patient were analyzed in this study (Table 1).

2.2. Overall system

Fig. 1 depicts the diagram of our seizure prediction tool (Aarabi and He, 2012). In brief, in the preprocessing stage, the iEEG data were band-pass filtered between 0.5 and 100 Hz using a 4th order digital Butterworth filter and notched to remove possible 50 Hz power line noise. Then, the iEEG data were divided into 10-s nonoverlapping segments. A set of six univariate and bivariate features including correlation dimension (CD), correlation entropy (CEN), noise level (NL), Lempel-Ziv complexity (LZC), largest Lyapunov exponent (LLE), and nonlinear interdependence (NI) were extracted from iEEG segments.

The time profiles of the features were first smoothed using a backward-moving-average filter of 5 min. For each patient, a simple thresholding procedure was then applied to the time profiles to determine significant changes in the values of the selected features in comparison with a baseline, defined as a reference period remote in time from any seizure. In this procedure for each channel, the mean (μ) and standard deviation (σ) of each feature were calculated over the feature values obtained from the baseline. For each patient, the feature values of the entire iEEG dataset were then scanned segment by segment, and the location and the feature values of the segments exhibiting values greater than ($\mu + \sigma$) or less than ($\mu - \sigma$) were saved and passed to the next stage.

To locate seizure precursors, a rule-based decision-making stage was used to reach a single decision for any epoch (multichannel iEEG segments) in two steps. First, a spatial combiner integrated the information from different channels on a feature-by-feature. In total, there were six spatial combiners acting on the univariate and bivariate features. At this stage, an epoch indicated a preliminary seizure precursor if N_{ch} channels (out of 6 for the univariate measures and out of 15 for the bivariate measure) exhibited significant changes in comparison with the reference period. In this case, a primary seizure prediction flag was raised for the epoch.

In the second step, a feature integrator integrated the information from different features for each EEG epoch. The feature integration was performed in two stages. Stage 1 included the feature integrator I operating on the primary flags at the output of the spatial combiners. At this stage, for each segment, if N_F primary flags showed significant changes above a predefined threshold (T_{c1}), a secondary flag was raised for the epoch indicating a higher probability for the epoch to be considered as a seizure precursor.