Noninvasive seizure prediction using autonomic measurements in patients with refractory epilepsy

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***Abstract*—There is resurgent interest in the role played by autonomic dysfunction in seizure generation. Advances in wearable sensors make it convenient to track many autonomic variables in patient populations. This study assesses peri-ictal changes in surrogate measures of autonomic activity for their predictive value in epilepsy patients. We simultaneously recorded fronto-central surface EEG and submental EMG to score vigilance state, intracranial EEG (iEEG) to compute several electrophysiological variables (EV), and measurements (heart rate, blood volume pulse, skin impedance, and skin temperature) relevant to autonomic function (AV) using a wrist-worn sensor from three patients. A naïve Bayes classifier was trained on these features and tested using five-fold cross-validation to determine whether preictal and interictal sleep (or wake) epochs could be distinguished from each other using either AV or EV features. Of 16 EV features, beta power, gamma power (30-45 Hz and 47-75 Hz), line length, and Teager energy showed significant differences for preictal versus interictal sleep (or wake) state in each patient (t test: $p < 0.001$). At least one AV was significantly different in each patient for interictal and preictal sleep (or wake) segments ($p < 0.001$). Using AV features, the classifier labeled preictal sleep epochs with 84% sensitivity, 79% specificity, and 64% kappa; and 78%, 80% and 55% respectively for preictal wake epochs. Using EV, the classifier labeled preictal sleep epochs with 69% sensitivity, 64% specificity, and 33% kappa; and 15%, 93% and 10% respectively for preictal wake epochs.**

***Keywords*- Epilepsy, Sleep-wake state, Noninvasive, Autonomic and Seizure prediction.**

I. Introduction

Epilepsy is a devastating neurological disorder marked by instances of abnormal electrical discharge in the brain and consequent loss of awareness termed seizures [1], and affects around 1% of the world's population. About 30% of epilepsy patients have seizures that are resistant to antiepileptic medication [2]. Surgical resection of epileptogenic brain tissue is sometimes an option for these patients [3] and has about a 60% chance of success, meaning that the patient becomes seizure-free after treatment [4]. Surgical outcomes depend on how accurately the seizure onset zone (SOZ) is localized and current diagnostic methods for predicting this region remain suboptimal [5]. Patients who do not benefit adequately from medication or surgery must live in constant dread of when the next seizure might strike. The technology, if available, for reliably predicting seizures and issuing a warning or delivering treatment would help patients avoid injury or fatality, reduce anxiety, and perhaps even indulge in normal activities like swimming or driving [6, 7]. Most seizure prediction approaches attempted to date extract univariate and/or multivariate features from iEEG signals and build statistical classifiers using training data sets to differentiate pre-ictal from interictal data [8-10]. However, the dependence on iEEG to predict seizures requires that a monitoring device be implanted to allow continuous tracking of brain state, an expensive prospect that may not be an option to many; any method capable of noninvasive seizure monitoring and prediction would without doubt be attractive to all concerned.

Various physiological measurements including surface electromyography (sEMG), electrodermal activity (EDA), electrocardiography (EKG), accelerometry (ACM), skin temperature (ST), and mattress pressure sensors are touted as non-invasive methods for detecting seizures [11]. In a couple of studies, EDA was found to increase dramatically with certain types of seizures [12, 13]. Heart Rate (HR) and its variability can change during and sometimes before seizures, suggesting utility for seizure detection [14, 15]. Other studies suggest that skin temperature changes may be correlated with and therefore useful for seizure detection [11].

In this pilot study, we tested the feasibility of seizure prediction using noninvasive measurements of autonomic nervous system function made during presurgical evaluation in three patients with refractory epilepsy and compared performance against iEEG-based prediction.

II. Methods

A. Data acquisition

Three patients admitted for invasive presurgical evaluation using video and iEEG at the University of Kentucky Medical Center were monitored continuously for 4-5 days each. With institutional approval and informed consent, frontocentral scalp EEG, submental EMG, and EKG were simultaneously recorded with the iEEG, all sampled at 1024 Hz, to help determine vigilance state. Four additional measurements relevant to autonomic function were made using a wrist-worn device (E4, Empatica): electrodermal activity (EDA; sampling rate = 4 Hz), heart rate (HR; 1 Hz), blood volume pulse (BVP; 64 Hz) and skin temperature (ST; 4 Hz).

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B. Determination of vigilance state

Several one hour-long interictal and preictal segments of iEEG and autonomic measurements were extracted. Each segment was further manually categorized as occurring in sleep or wakefulness by reviewing the video-EEG data. This allowed the analyses to be done separately for wake and sleep data to minimize the potentially confounding effect of vigilance state on the results.

To further verify that the segments were correctly labeled as sleep or wake, they were compared using electrophysiologically derived "sleep features" that reflect changes in vigilance state. Since the surface EEG turned out to be unreliable (poor signal quality), the sleep features used were spectral band power ratios *S1* = *delta*/*theta* and *S2* = (*alpha*+*sigma*+*beta*+*gamma*)/(*delta*+*theta*), where delta = delta1+delta2, based on frequency bands delta1 (0.5-2 Hz), delta2 (2-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-55 Hz) bands [16, 17]. The mean-squared value of the submental EMG was used as a third sleep feature. All three features were estimated in 30-second long non-overlapping windows with smooth filtering to avoid boundary effects. *S1* and *S2* were derived from iEEG contacts as close to frontocentral locations as possible.

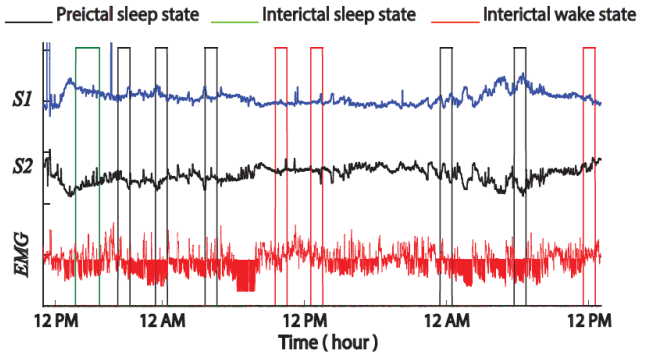

Figure 1. Time series of sleep features *S1*, *S2* and r.m.s. EMG measured in 30-s non-overlapping windows for Patient 1. One hour epochs of preictal and interictal wake and sleep epochs identified by manual review of video-EEG are denoted by vertical bars (no preictal wake segment was available for Patient 1).

C. Interictal vs. preictal differences in iEEG features and noninvasive autonomic measurements

Seven interictal and preictal segments were identified during sleep from patient 1; six interictal and preictal segments during sleep, and eight interictal and five preictal segments during wakefulness from patient 2; and eight interictal and three preictal segments during wakefulness from patient 3. Hence two of three patients had either only sleep or only wake data.

Bipolar derivations from iEEG contacts were used to extract several electrophysiological variables (EVs) for seizure prediction. This set of linear and nonlinear signal features ─ signal power in the *delta*, *theta*, *alpha*, *beta*, and three different *gamma* [30-45 Hz, 45-75 Hz, 75-100 Hz] bands; and the mean, standard deviation, skewness, kurtosis, decorrelation time (DT), autoregressive error (AR), Teager energy (TE), line length (LL), and approximate entropy (ApEn) computed with an embedding dimension of 2, tolerance of 0.2 SD, and delay of 1 ─ were estimated in 5-sec long non-overlapping windows from one bipolar iEEG derivation located in the putative SOZ (as marked by the neurologist based on imaging and ictal/interictal activity). In addition, mean values of the noninvasive measurements EDA, HR, BVP, and ST were computed in 5-sec long non-overlapping windows to give a set of four *autonomic* variables (AV). All analysis was performed offline using Matlab™ (Mathworks, Natick, MA).

A naïve Bayes classifier was trained separately on sample data and tested using five-fold cross-validation to determine whether preictal and interictal epochs could be distinguished from each other using either AV or EV features. The test was done separately for sleep and wake data. For the EV feature set, interictal and preictal training samples in each fold were reduced to the three most promising variables using a feature selection technique, known as the ReliefF algorithm [18], for classification of test data; for the AV feature set all four AVs were used without exception.

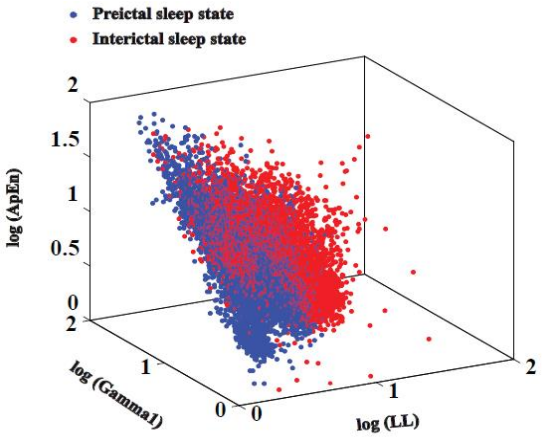

Figure 2. Scatter plot of the three most influential iEEG features for interictal vs. preictal state classification (during sleep) in patient 1.

III. Results

Fig. 1 shows that the manually scored vigilance state label in each one-hour segment is consistent with relative values of sleep features *S1*, *S2* (estimated from iEEG) and submental EMG power: samples with high *S1*, low *S2*, and low EMG correspond to sleep, and samples with low *S1*, high *S2*, and high EMG to wakefulness.

A naive Bayes classifier constructed using the three most significant EV features selected by the Relief algorithm from training data (see Fig. 2), labeled preictal sleep epochs with 69% sensitivity, 64% specificity, and 33% Cohen's kappa; and preictal wake epochs with 15%, sensitivity 93% specificity, and 10% kappa respectively. The features most commonly selected across the three patients by the ReliefF algorithm were beta, gamma1, gamma2, LL, TE and ApEn regardless of the vigilance state, as shown in Table I.

At least one AV differed significantly for interictal and preictal sleep segments, and between interictal and preictal

wake segments (t test; $p < 0.001$); for instance, see EDA and ST of patient 1 during sleep (Figs. 3, 4). Five-fold cross-validation showed that an AV classifier labeled preictal sleep epochs with 84% sensitivity, 79% specificity, and 64% kappa; and preictal wake epochs with 78% sensitivity, 80% specificity, and 55% kappa, respectively (see Table II).

Approach	*Patient ID*	*State*	*NIS*	*NPS*	*SE %*	*SP %*	*Kappa %*	*Most Influential features*
EVs	P1	W	5	NA	NA	NA	NA	NA
		S	7	7	84	57	40	LL, gamma1, and ApEn
	P2	W	8	5	2.8	97	0.8	LL, gamma2, and TE
		S	6	6	54	71	25	Beta, gamma1, and Std
	P3	W	8	3	27	88	18	gamma1, gamma2, and gamma3
		S	8	NA	NA	NA	NA	NA
Average		S	13	13	69	64	33	
		W	16	8	15	93	10	

Table I. Preictal versus interictal classification using iEEG features (EV). The table reports classification accuracy in terms of sensitivity (SE), specificity (SP), and Cohen's kappa. NIS and NPS are the number of interictal and preictal segments available, respectively, for each patient. The most influential features listed are based on the ReliefF algorithm.

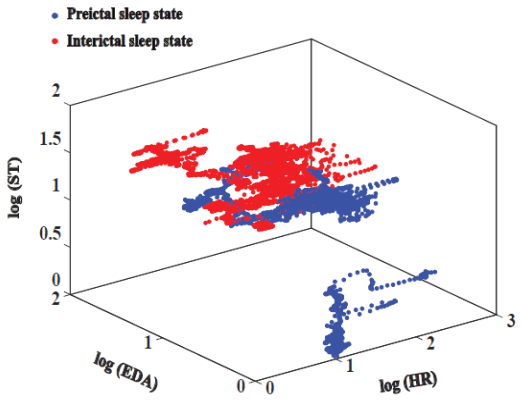

Figure 3. Scatter plot of the three autonomic variables with the greatest contrast between interictal and preictal sleep states in patient 1. Each data point is estimated from a 5-second epoch.

IV. Discussion

The purpose of this study was to test whether noninvasive sensors that track autonomic function can be used to predict epileptic seizures. The tests employed features of these measurements to classify preictal and interictal samples of data. Performance was compared against classifiers trained on iEEG features extracted from the same data.

Approach	*Patient ID*	*State*	*NIS*	*NPS*	*SE %*	*SP %*	*Kappa %*	*Most Influential features*
AVs	P1	W	5	NA	NA	NA	NA	NA
		S	7	7	90	94	85	EDA and ST
	P2	W	8	5	75	71	44	EDA
		S	6	6	78	64	43	HR
	P3	W	8	3	80	88	65	HR and ST
		S	8	NA	NA	NA	NA	NA
Average		S	13	13	84	79	64	
		W	16	8	78	80	55	

Table II. Preictal versus interictal classification using autonomic measurements (AV). The most influential features were listed here based on the greatest contrast between interictal and preictal sleep (or wake) states.

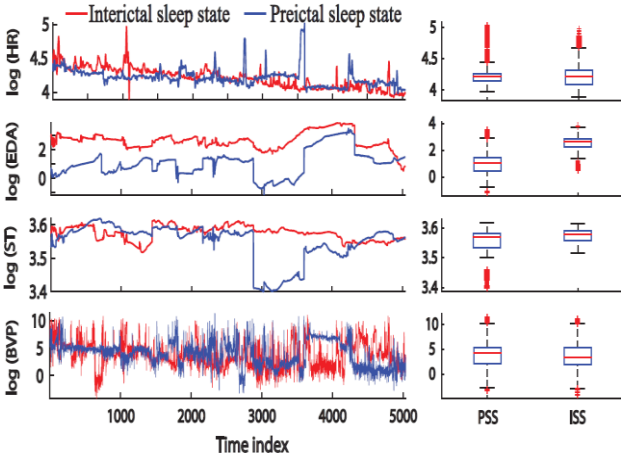

Figure 4. Left: Time trends in autonomic variables concatenated for seven one-hour long interictal and preictal sleep states (ISS and PSS) in Patient 1. Note: each time point represents a 5-sec mean value. **Right:** Box plots comparing preictal and interictal values of each variable.

In general, we found that at least one autonomic variable, most commonly EDA (for instance, see data for patient 1 in Fig. 4) and sometimes HR, was significantly different in value between interictal and preictal sleep or (wake) states. ST also seemed promising in some instances and including it may have helped improve performance. In general, the combination of these four noninvasive autonomic measurements seems to have produced good classification outcomes.

Some previous studies with wearable sensors in epilepsy [19-21] have used autonomic measurements, but mainly for seizure detection, not prediction; moreover, none appear to have included skin temperature as a predictor. Finally, these studies did not account for the effects of vigilance state changes.

In our investigation, we performed separate tests for sleep and wake data to avoid the potentially confounding effects of vigilance state on the outcomes, since autonomic nervous

system function is modulated by vigilance state. To minimize the possibility of errors in manual sleep/wake scoring, we verified vigilance state in each one-hour segment of analyzed data by examining trends in electrophysiologically derived sleep features *S1*, *S2*, and *EMG* (see Fig. 1). Our results show that both methods were consistent with each other.

For lack of a better gold standard, the performance of the AV classifiers was compared against that of classifiers constructed from multiple iEEG features (EV) commonly used in the seizure prediction literature [22, 23]. Surprisingly, the AV method outperformed iEEG almost across the board. Although this is a favorable outcome, since the AV measurements are noninvasive, a couple of possible explanations that must first be ruled out. Firstly, this is a small sample, only three patients. Results of data collection and analysis in a larger cohort, which is ongoing, must be considered before making any generalizations. Second, the iEEG segments from each subject were derived from only one bipolar derivation within the SOZ, and the choice may have not been optimal. Including more iEEG contacts inside and outside the SOZ could possibly have improved prediction but the iEEG approach is invasive nonetheless. Selecting only the top three EV features based on the ReliefF algorithm (see example shown in Fig. 2) did improve performance but not enough to be considered good classification. A point of interest is that gamma1 and gamma2 bands were the features most commonly selected in all patients, which mirrors the findings of Park et al, 2011 [23]. Thirdly, this analysis was performed on isolated one-hour segments. It is possible that running the classifiers on continuous data over several days might generate false positives that alter the results.

V. CONCLUSION

The results of this study suggest that autonomic changes may be predictive of epileptic seizures in certain individuals, even after correcting for differences in vigilance state. Appreciable peri-ictal changes were documented in EDA, ST, and HR, all of which are easily measured using noninvasive wearable sensors. While these observations are encouraging, they are preliminary results from an ongoing study and need to be verified in a larger sample and with continuous classification of seizure and non-seizure data over long timeframes rather than of isolated interictal and preictal samples. These limitations will be addressed in future work.

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