

Transient behavior of cardiorespiratory interactions towards the onset of epileptic seizures

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Abstract

Epileptic seizures are typically related to autonomic dysfunction. During seizures, the cardiac and respiratory mechanisms are deeply affected. This effect of epilepsy can also occur a few seconds before the seizure onset in the EEG. In addition, the interaction between respiration and heart rate is also expected to be affected. This study aims to determine whether the cardiorespiratory interactions change during seizures, and more importantly if they show a transient behavior towards the seizure onset. This is done by means of a time series method based on entropy decomposition applied to ECG and respiratory data. Here, the information carried by the heart rate that can be predicted by its own past, or by the past of the respiration, or by a combination of the two, is quantified. It is shown that cardiorespiratory interactions also change even before the onset of focal, and absence seizures. This suggests that early detection of focal seizures can be improved, and that detection of seizures without a clear effect on the heart rate (i.e. absence) can also be detected. In tonic/tonic-clonic seizures no consistent significant change in the autonomic controls was found.

1. Introduction

Epilepsy is closely related to dysfunction of the cardiac and respiratory control mechanisms of the autonomic nervous system [1]. It is well known that epileptic seizures are not only accompanied by motor activity and stress responses, but also by different autonomic changes, such as tachycardia, bradycardia and hyperventilation. Cardiac changes are thought to be caused by the propagation of epileptic discharges to the central autonomic network [1], which on its turn influences the output of the respiratory control mechanisms [2]. The presence of ictal (during seizures) cardiac disturbances has been reported in sev-

eral studies [1][3]. In fact, these disturbances can also occur seconds before (pre-ictal) or after (post-ictal) the EEG changes marking the onset or offset of the seizure [2][4]. Here, the focus is on pre-ictal changes, and they can be seen as autonomic symptoms, or the first manifestations of seizures. Therefore, they constitute an important factor for the development of early detection systems.

As mentioned before, respiratory changes have also been observed during different types of seizures. For example, in [5] it was reported that seizures generated from the temporal lobe are typically accompanied by episodes of apnea. However, it is not yet understood whether apnea is secondary to the seizure, or if cardiac changes result as a response to oxygen desaturation caused by apnea [1]. It is certain, in any case, that there is a direct and profound effect of epilepsy on the cardiorespiratory control. Furthermore, the coupling between respiration and heart rate is thought to be affected due to deep involvement of autonomic centers during seizures. With this in mind, the question is whether cardiorespiratory interactions change “before” the EEG onset. And if this is the case, whether these changes show a transient behavior towards the seizure onset. In this work, these two hypotheses are addressed by means of the quantification of information dynamics [6].

2. Methodology

2.1. Data description and pre-processing

The dataset used in this study consists of single-lead ECG (lead II) recordings extracted from continuous 24-hour video-EEG monitoring of 37 children admitted to the epilepsy clinic of UZ Leuven, Belgium. The mean age of the patients was 9.2 years (range 3-16 years), they were all suffering from refractory epilepsy, and none of them was receiving any drug with chronotropic action. In total, 87 seizures were recorded, of which 48 were of focal na-

ture, with 28 originated from the frontal lobe (FLE) and 20 from the temporal lobes (TLE), and 39 were generalized seizures. The latter group includes 10 generalized absence seizures (GAB), and 29 tonic or tonic-clonic seizures (GTN). The onsets of the seizures were annotated by two different EEG specialists based on video and EEG.

In addition to the ECG recordings, the respiratory efforts measured around the abdomen (R_a) and thorax (R_t) are also available for 18 seizures (8 FL, 10 GAB). The sampling frequency for both the ECG and respiration is 250Hz.

Each ECG recording is used to compute the RR-interval time series (RRI), and two ECG-derived respiratory signals, namely, one using principal component analysis (EDR_l)[7], and another one using its non-linear version (EDR_k)[8]. The Rpeaks are located using the Pan-Tompkins algorithm, and ectopic and missing beats are corrected by means of a search back procedure as in [2]. When the respiratory signals are available, they are first low-pass filtered at 2Hz, and then resampled using the position of the Rpeaks in the corresponding ECG signals. All signals, RRI , R_a , R_t , EDR_l and EDR_k are filtered using a high-pass filter at 0.05Hz in order to remove low frequency oscillations that are not related to respiration.

2.2. Information dynamics

The cardiorespiratory interactions are quantified by means of a time series method based on information dynamics [6]. Here, this method is applied on the signals described above, and interactions between each respiratory signal (real or estimated) and the heart rate are assessed.

Let us consider a stationary stochastic process $U = [X, Y]$, with X_n and Y_n the observations of U at time n . Here, Y_n corresponds to the present of RRI , which is driven by changes in respiration (X_n). The respiration can be described by approximations like EDR_l and EDR_k , or by real measurements like R_a and R_t , when available. In order to quantify how much information is shared between Y_n and its own past $Y_n^- = [Y_{n-1}, Y_{n-2}, \dots]$, and the past of the driver signal $X_n^- = [X_{n-1}, X_{n-2}, \dots]$, the *predictive information* (P_Y) can be computed as

$$P_Y = H(Y_n) - H(Y_n | X_n^-, Y_n^-). \quad (1)$$

Note that P_Y can be computed by subtracting the *conditional entropy* of Y_n knowing the past of U , from the *Shannon entropy* of Y_n . By including the conditional entropy of Y_n knowing only the past of one of the two variables in U , one can compute P_Y using the following expressions:

$$P_Y = H(Y_n) - H(Y_n | Y_n^-) + H(Y_n | Y_n^-) - H(Y_n | X_n^-, Y_n^-), \quad (2)$$

or,

$$P_Y = H(Y_n) - H(Y_n | X_n^-) + H(Y_n | X_n^-) - H(Y_n | X_n^-, Y_n^-). \quad (3)$$

In (2), $H(Y_n) - H(Y_n | Y_n^-)$ corresponds to the *self entropy* (S_Y), which is the information carried by Y_n that can be predicted from its own past, and $H(Y_n | Y_n^-) - H(Y_n | X_n^-, Y_n^-)$ refers to the *transfer entropy* ($T_{X \rightarrow Y}$), which describes the amount of information carried by Y_n that can be predicted by the past of X_n without taking into account the past of Y_n . In (3), the amount of information in Y_n predicted from the past of X_n is described by the first term, which corresponds to the *cross-entropy* ($C_{X \rightarrow Y}$), and the residual amount of information in Y_n retrieved by its own past is quantified by the *conditional self entropy* $S_{Y|X}$. All the entropy terms mentioned above are computed by means of the covariance matrix, as stated in [9] and applied to Gaussian distributed variables [10]. The Akaike information criterion was used to determine the model order in this implementation.

On the one hand, when the amount of information transferred from the respiration to the heart rate is large, the values of $C_{X \rightarrow Y}$ and $T_{X \rightarrow Y}$ are expected to be also large. This can be interpreted as the strong modulation of the heart rate produced by the respiratory sinus arrhythmia. On the other hand, when the heart rate is more predictable, which can be seen as a limiting factor to react to acute situations like seizures, the values of $S_{Y|X}$ and S_Y are expected to be large. In other words, the amount of information carried by the heart rate that can be predicted from its own past is large. The main difference between $S_{Y|X}$ and S_Y is that $S_{Y|X}$ describes the influence of physiological mechanisms, other than respiration, that produce a more predictable heart rate, while S_Y may also incorporate respiratory influences.

2.3. Dynamic computation of cardiorespiratory interactions

In order to determine whether there is a transient behavior in the cardiorespiratory coupling before/during the seizures, it is important to consider the non-stationary nature of the signals, especially around seizure activity. Keeping this in mind, a moving window of 100 heart beats (HB) with an overlap of 99 HB is used to analyze the data. For each window, a set of entropy values $\mathcal{S}_{ri} = [C_{X \rightarrow Y}, S_{Y|X}, T_{X \rightarrow Y}, S_Y]$ is computed, with $r = [EDR_l, EDR_k, R_a, R_t]$, $i = 1, \dots, N$, and N the total number of windows in the signal.

3. Results and discussion

For the analysis, segments of 5 minutes were extracted from the dataset, starting 3 minutes before the seizure onset. Following the procedure described above, N sets of entropy parameters $\{\mathcal{S}_{ri}\}_{i=1}^N$ were computed for each pair $[RRI, EDR_l]$, $[RRI, EDR_k]$, $[RRI, R_a]$, $[RRI, R_t]$, considering that the last two pairs were only available for 18

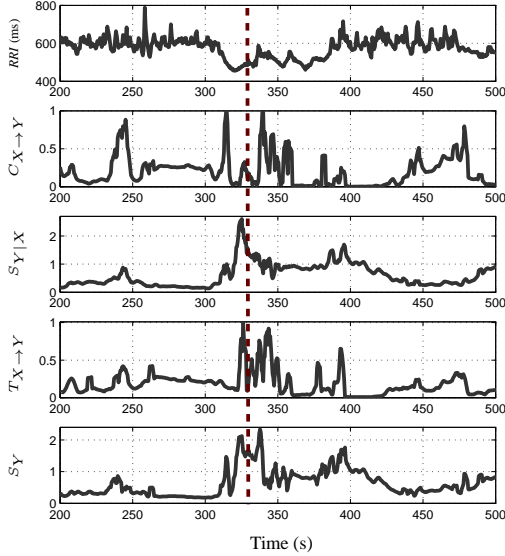


Figure 1. Information dynamics analysis of a RRI segment around a generalized seizure. The red dashed line indicates the onset of the seizure in the EEG. Note that the heart rate changes even before the EEG onset, and interactions between respiration and heart rate, are also affected by the seizure.

seizures. These sets were computed for all 87 ECG segments.

In Figure 1 it is shown that there are indeed transient changes in the amount of information transferred from respiration to heart rate. Furthermore, it can be seen that these changes start occurring before the seizure onset in the EEG, which means that these can be used for early detection of epileptic seizures, even when no “obvious” changes in heart rate are present. In order to quantify the changes in cardiorespiratory interaction around the seizures, the mean value for each entropy parameter was computed in a window of 60s around the seizure onset. This value was then compared with the one computed from a window of 60s in a seizure-free region. Differences between these values were evaluated with a confidence interval of 95% using the Kruskal-Wallis test.

It turns out that the interactions between respiration and heart rate depend on the type of seizure. Hence, the findings for the two types of seizures will be described separately in more detail below.

3.1. Focal seizures

Figure 2 shows the self entropy S_Y (left panel) and the conditional self entropy $S_{Y|X}$ (right panel) for four different respiratory signals ($EDR_l, EDR_k, R_a,$ and R_t). The values of S_Y and $S_{Y|X}$ for segments around the seizures (light grey boxplots) are compared with the values of S_Y and $S_{Y|X}$ within a normal segment (dark grey). Note

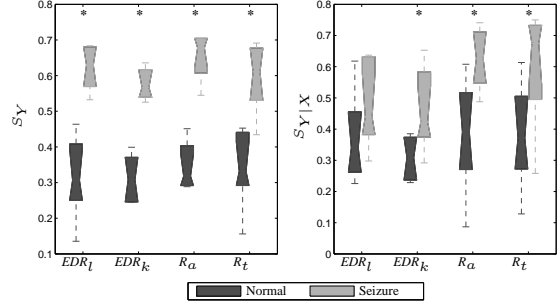


Figure 2. Self entropy S_Y and self conditional entropy $S_{Y|X}$ values around the seizure onset, and during seizure-free activity. Four different respiratory signals were used, and significant differences are indicated by (*). Note that the discrimination of epileptic seizures is enhanced when the amount of information shared between the present of the heart rate, and its own past without removing respiratory influences (i.e. S_Y), is used.

that the information shared between heart rate and its own past (S_Y) is significantly different around the onset, which means that a more predictable heart rate is present around seizures. This has already been investigated in previous studies [4][5], where it was shown that this effect is more significant for TLE. However, here it is observed that the seizures originated from the frontal lobe, are also accompanied by highly predictable heart rates, and can be easily classified using these values of entropy.

An important observation is the predictive role of respiration. This can be seen when S_Y (left panel) is compared with $S_{Y|X}$ (right panel), as the differences are not as significant anymore when influences of respiration are removed (i.e. $S_{Y|X}$). Furthermore, it is remarkable that clear separations can be obtained even with an ECG-derived respiratory signal, which can be important in applications where a limited amount of sensors is available.

An explanation for these changes in cardiorespiratory information dynamics in TLE and FLE, can be found in the anatomic localization, relative to the central autonomic network, of the temporal and frontal lobe structures [2]. This proximity allows for the propagation of epileptic discharges from one of these lobes to the central autonomic network, which can result in cardiac and respiratory disturbances.

3.2. Generalized seizures

A different situation is observed for generalized seizures. Here a distinction is made between tonic/tonic-clonic, and absence seizures. Figure 3 shows that the amount of information shared between the past of respiration and the present of RRI (i.e. $C_{X \to Y}$ and $T_{X \to Y}$) is significantly reduced in absence seizures. This is an im-

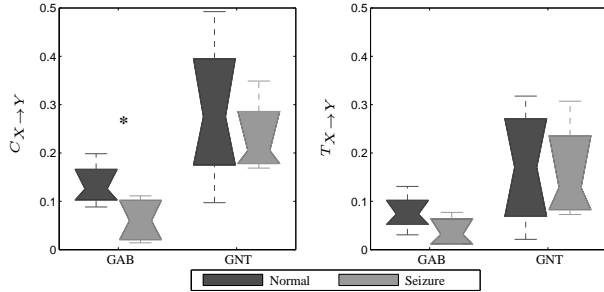


Figure 3. Cross entropy $C_{X \rightarrow Y}$ and transfer entropy $T_{X \rightarrow Y}$ for regions around absence seizures and generalized tonic/tonic-clonic seizures, compared with values for seizure-free regions. The respiratory signal used in this case corresponds to EDR_k . However, the results do not differ significantly when a different respiratory signal is used. The significant difference is indicated by (*).

portant finding, since this type of seizures do not show a consistent effect on the heart rate [2]. The later can be confirmed from the measurements of $S_{Y|X}$, during absence seizures. A slight increase in the residual information explained by physiological parameters, other than respiration, is observed. However, this increase is not significant, which is in agreement with previous findings reported in the literature [5]. The reason why the respiration plays a significant role in this type of seizures can be explained by the involvement of the thalamocortical network in absence epilepsy [2].

Concerning tonic/tonic-clonic seizures, no significant differences were found. This is not a surprise, since this type of seizures are characterized by motor activity, which needs to be considered when recording signals like the ECG. For this reason, other modalities need to be taken into account to be able to find physiological changes that may lead to this type of seizures.

4. Conclusion

This study shows that the cardiorespiratory interactions are significantly affected during seizures, but more importantly, they show a transient behavior towards the seizure onset. This allows for early detection of epileptic seizures, which can contribute to the improvement of closed-loop systems like vagus nerve stimulation (VNS), and to the development of alarm systems and more accurate drug-delivery mechanisms.

It was also shown that absence epilepsy has a profound effect on the cardiorespiratory interactions, which represents an important finding for patients suffering from this type of epilepsy. Future studies will include the validation of these results on a bigger dataset, and the complete analysis in adult epilepsy.

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