Interictal Cardiorespiratory Variability in Temporal Lobe and Absence Epilepsy in Childhood

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***Abstract*— It is well known that epilepsy has a profound effect on the autonomic nervous system, especially on the autonomic control of heart rate and respiration. This effect has been widely studied during seizure activity, but less attention has been given to interictal (i.e. seizure-free) activity. The studies that have been done on the latter, showed that heart rate and respiration can be affected individually, even without the occurrence of seizures. In this work, the interactions between these two individual physiological mechanisms are analysed during interictal activity in temporal lobe and absence epilepsy in childhood. These interactions are assessed by means of an entropy decomposition that allows to split the information carried by the heart rate, into two main components, one related to respiration and another related to different mechanisms. It is shown that in absence epilepsy the information shared by respiration and heart rate differs significantly from normal conditions.**

I. INTRODUCTION

It is well known that the cardiorespiratory controls of the autonomic nervous system are deeply affected by epileptic seizures [1]. For example, in temporal lobe epilepsy (TLE), seizures are associated with episodes of apnoea [2], during which the heart rate (HR) and the respiration are significantly altered. In a different type of epilepsy, namely absence epilepsy (AE), seizures do not seem to have any particular effect, however, a more interesting effect is observed during interictal (seizure-free) activity. The heart and respiratory rate appear to be distorted even without the occurrence of an epileptic seizure [3]. This could possibly be explained by a different connectivity in the brain when compared to normal subjects. Furthermore, these distortions might play a key role in the pathophysiology of sudden unexpected death in epilepsy (SUDEP).

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Several studies have been conducted on autonomic dysfunction during seizures, however, limited attention has been given to seizure-free periods in epilepsy. For example, in [3] this was studied, but the heart rate and the respiration were analysed separately. As mentioned before, it was found that children suffering from AE showed deviations, both in the heart rate and the respiration, that were not related to seizure activity. This raises the interesting question whether or not the cardiorespiratory interactions are also affected. In this study, this question is addressed by means of a time series method based on information dynamics [4].

II. DATA

Single-lead ECG signals were extracted from 24h video EEG recordings, from 10 children with absence epilepsy (mean age 10.0±1.9 years), 10 children with temporal lobe epilepsy (mean age 10.3±2.7 years), and 10 control subjects (mean age 10.8±4.3) denoted respectively by AE, TLE and CO. None of the subjects was known to suffer from a cardiac nor a respiratory problem. The ECG signals were recorded with a sampling frequency of 250Hz, and they were segmented using the annotations provided by two independent EEG specialists, who indicated the start and end of each epileptic seizure. In order to capture the interictal activity, ECG epochs of 5 minutes were selected after satisfying two conditions: no seizure activity is present, and the onset of any seizure is at least 30 minutes away. In total 30 segments (one per subject) were selected.

From each ECG epoch, the RR interval time series and the ECG-derived respiration (EDR) were computed. The R-peaks were detected using the Pan-Tompkins algorithm, and verified by manual inspection. The EDR signal was computed by means of kernel principal component analysis (kPCA) [5]. The resulting signals were filtered using a high-pass Butterworth filter with cutting frequency at 0.05Hz.

III. METHODOLOGY

Assume a stationary stochastic process $U = [X, Y]$, where X_n corresponds to the present of the EDR signal, and Y_n the present of the RR interval time series, with time n. The *predictive information* is an estimation of how much information carried by Y_n can be predicted by $Y_n^- = [Y_{n-1}, Y_{n-2,\ldots}]$ (i.e the past of Y up to time $n-1$) and the past of X which is denoted as $X_n^- = [X_{n-1}, X_{n-2}, \ldots]$, and is expressed as:

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

The first term corresponds to the *Shannon entropy* of Y_n, and the second refers to the *conditional entropy* of Y_n knowing

the past of the process. The definition in (1) can be rewritten as:

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

where $H(Y_n) - H(Y_n|X_n^-)$ refers to the *cross-entropy* $C_{X\to Y}$, which is the amount of information shared between Y_n and the past of X. When there is a large amount of information transferred from the respiration to the heart rate, one expects this value to be also large. In (2), $H(Y_n|X_n^-) - H(Y_n|X_n^-, Y_n^-)$ corresponds to the *conditional self entropy* $S_{Y|X}$, and quantifies the residual amount of information that can be retrieved from the past of Y. In this case, $S_{Y|X}$ quantifies all variations in heart rate that could not be explained by respiration but are explained by its own past. As such, it reflects physiological mechanisms, different from respiration, producing predictable heart rate dynamics. The advantage of this decomposition is that it is possible to split the information carried by heart rate into two components: respiration and others (e.g. sympathetic activation). For details on this decomposition, see [4]. The values of $C_{X\to Y}$ and $S_{Y|X}$ were computed using the covariance matrix, according to a definition adopted in [6] and valid for Gaussianly distributed variables [7].

IV. RESULTS AND DISCUSSION

The information decomposition described in the previous section was computed for each subject and each pair of signals, namely RR interval time series and EDR. The differences between the entropy estimations of different groups (AE, TLE and CO) were evaluated using the Kruskal-Wallis and multicomparison tests. Figure 1 shows the different entropy values. Note that the cross-entropy values for the AE group are significantly lower than those of the control group. This means that the influence of respiration on the HR is affected, which confirms that not only respiration itself is altered in this type of epilepsy. As mentioned in the introduction, a possible explanation can be a modification of the connectivity in the brain, and/or the influence of higher sympathetic activation. In AE seizures, the thalamocortical network, which is the connectivity between the thalamus and the cerebral cortex, is deeply involved [8]. This network could be more sensitive to changes in AE, causing a long term alteration to the respiratory control mechanism. This is of course a hypothesis that needs to be confirmed in further studies.

Additionally, it can be seen that the TLE group is more similar to the control group, which is an indication that TLE affects the cardiorespiratory interaction less than AE. This is in agreement with previous findings [3].

Concerning the self conditional entropy, it is observed that for control cases, there is less information shared between the heart rate and its past, which means that there is more HR variability, which allows for faster reaction on acute changes. This effect is more pronounced in AE group, which also confirms that there is an interictal autonomic alteration in this kind of patients.

V. CONCLUSIONS

This study shows that there are some autonomic differences between AE and CO during seizure-free activity.

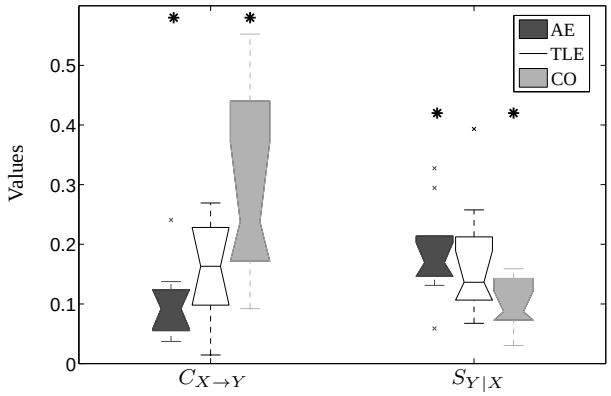


Fig. 1. Boxplots of cross-entropy $C_{X\to Y}$, and self conditional entropy $S_{Y|X}$ for the three groups under investigation: absence epilepsy (AE), temporal lobe epilepsy (TLE) and control group (CO). Note that both values are significantly different (indicated by *****) between AE and CO. This is an indication of an increased autonomic dysfunction in AE. The TLE group displays a less severe alteration to the autonomic controls, and it resembles better the properties of the control group.

Patients suffering from AE display a less adaptive heart rate and a modified cardiorespiratory interaction. This new insight might indicate a deeper underlying reason that is maybe not yet fully understood, such as for example the brain connectivity in absence epilepsy. Further research is needed to unravel the fundamental cause.

This approximate method is a convenient and fast way to describe the linear interactions between respiration and heart rate. Using the exact formula for the entropy would take into account non-linear interactions, but this latter method is more demanding and prone to overfitting for short and noisy time series. However, non-linearities may need to be taken into account, since the dynamics of the cardio respiratory system might be more complex.

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