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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 this topic, 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 variables are analysed during interictal activity in temporal lobe and absence epilepsy in childhood. These interactions are assessed by decomposing the predictive information about heart rate variability, into different components like the transfer entropy, cross-entropy, self- entropy and the conditional self entropy. Each one of these components quantifies different types of shared information. However, when using the cross-entropy and the conditional self entropy, it is possible to split the information carried by the heart rate, into two main components, one related to respiration and one related to different mechanisms, like sympathetic activation. This can be done after assuming a directional link going from respiration to heart rate. After analysing all the entropy components, it is shown that in subjects with absence epilepsy the information shared by respiration and heart rate is significantly lower than for normal subjects. And a more remarkable finding indicates that this type of epilepsy seems to have a long term effect on the cardiac and respiratory control mechanisms of the autonomic nervous system.

1. INTRODUCTION

Epilepsy is a brain disorder characterized by the occurrence of unprovoked seizures, which are synchronous or abnormal neuronal discharges that may affect different regions of the brain (Fisher et al. 2005). Different factors can be related to the origin of seizures,

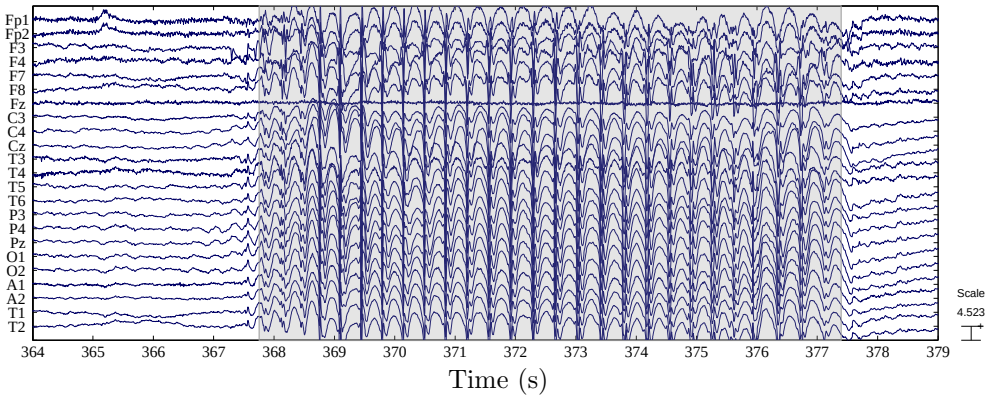


Figure 1. EEG of a typical absence seizure. The high amplitude spike-and-wave complexes are indicated inside the shaded area. These oscillations have a frequency larger than 2.5Hz and they propagate throughout the whole brain. Note that the channel Fz located in the frontal area is not showing the same pattern. This is not related to the propagation of the epileptic discharges but to the malfunctioning of the channel during the whole monitoring period.

for instance, brain injury, brain tumor, stroke, structural or metabolic disorder of the brain, and genetic factors, amongst others. However, in most of the cases the causes are unknown (Berg et al. 2010).

Seizures can be classified into two main groups, namely, focal and generalized seizures (Berg et al. 2010). Focal seizures originate from one particular region and may or may not spread throughout the whole brain causing a secondary generalization. Generalized seizures on the other hand, involve spike-and-wave discharges in the whole brain, and most likely result in loss of consciousness (Blumenfeld 2005). The manifestations of the seizures closely depend on the location of the epileptic discharges. For example, seizures affecting the motor cortex can manifest as convulsions, trembling, jerking or rapid contraction/extension of the muscles. These are the types of seizures that are most commonly associated with epilepsy. However, there are other types of seizures with many other manifestations that are not "clearly distinguishable" and can be unnoticed by a third person (e.g., care giver). This is the case in absence epilepsy (AE), which is characterized by generalized seizures that manifest themselves as impairment of consciousness and sometimes as staring. Absence seizures are more common during childhood, they last only few seconds, and they can occur several times per hour. Another important characteristic of this type of seizures is that high amplitude spike-waves discharges at frequencies larger than 2.5Hz can be observed in all channels of the EEG, as shown in Fig. 1. The fact that these seizures are unnoticeable by a third person makes it difficult to track the frequency of the seizures and to assist the patients when seizures occur.

A different type of seizures with *mild* manifestations corresponds to the complex-partial seizures in temporal lobe epilepsy (TLE). These seizures receive the name of complex-partial because they also cause impairment of consciousness and most of the

times they do not result in secondary generalization (Englot & Blumenfeld 2009). Furthermore, partial seizures in TLE can be accompanied by lip smacking, chewing, involuntary but coordinated movements, and they can last between 30s up to 2min.

It is well known that seizures are responsible for cardiovascular, cardiorespiratory and gastrointestinal changes (Devinsky 2004). Regarding the cardiorespiratory changes, seizures deeply affect the controls of the autonomic nervous system (O'Regan & Brown 2005). For example, in TLE, seizures are associated with episodes of apnea (Blumhardt et al. 1986), during which the heart rate (HR) is significantly increased while the respiratory rate decreases. In Singh et al. (2013) it was concluded that the younger the patient, the higher the probability to have apnea episodes. However, this can also be influenced by the amount of anti-epileptic drugs (AED) the patients were receiving. Moreover, in Seyal et al. (2010) it was shown that patients with TLE do not always develop apnea episodes, but still they can reach low values of oxygen saturation (SpO_2). This desaturation can be due to hypoventilation and result in sudden unexpected death in epilepsy (SUDEP) due to their inability to recover after an epileptic seizure. On the other hand, absence seizures do not seem to have any particular effect on the cardiac and respiratory functions. 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. This could possibly be explained by a different connectivity in the brain when compared to normal subjects (Jansen et al. 2013). Furthermore, these distortions might play a key role in the pathophysiology of SUDEP.

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 Jansen et al. (2013) and Varon et al. (2012) 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. If this is the case with patients suffering from epilepsy, it is possible to think that the mechanisms responsible for regulating central nervous functions, like arousal, are deeply affected. And this on its turn is closely associated with SUDEP.

This study investigates the differences in the cardiorespiratory interactions between patients with epilepsy and control subjects. Here, two types of epilepsy are studied, namely, AE and TLE in childhood. The heart rate and respiratory signals are derived from ECG recordings, and the cardiorespiratory interactions are assessed by means of a time series method based on information dynamics (Faes & Porta 2014).

The remaining of this document is organized as follows. Section 2 describes the dataset used in this study, and the methodology adopted here to quantify the interactions between heart rate and respiration. Section 3 presents the results and the observations, which are then discussed in section 4. Conclusions are presented in section 5.

2. METHODS

2.1. Data

Single-lead ECG (lead II) signals were extracted from 24h video-EEG-ECG 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. These patients were remitted to the epilepsy clinic of UZ Leuven in Belgium. Epilepsy patients needed a 24h video-EEG to assess the effect of therapy, and control subjects were suspected to suffer from epilepsy, but they were all found to be normal. None of the subjects was known to suffer from a cardiac nor a respiratory problem, and all patients were suffering from refractory (drug-resistant) epilepsy.

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 of each epileptic seizure. According to the guidelines presented in Malik et al. (1996), the recommended range for heart rate variability analysis is defined from 250Hz to 500Hz. However, in order to increase the precision of the R-peak locations the ECG was upsampled to 500Hz using cubic spline interpolation.

In order to capture the interictal activity, ECG epochs of 5 minutes were selected satisfying two conditions:

(i) No epileptic discharges are observed in the EEG

(ii) The onset of any seizure is at least 30 minutes away.

In total 30 segments (one per subject) of interictal activity, were selected. These segments were selected during the same time of the day, namely between 13h and 15h, and during this time the children were awake and at ease on their beds.

2.2. Data processing

From each ECG epoch of 5 minutes, 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. Due to the absence of recorded respiratory signals, breathing activity was derived from the ECG exploiting the well known respiration-induced modulation of QRS amplitude (Moody et al. 1985). While this approach yields only an approximation of respiratory activity, techniques for computation of EDR are widely used and have been validated thoroughly (Moody et al. 1986, Langley et al. 2010, Widjaja et al. 2012). In this study, the accurate reconstruction proposed by Widjaja et al. (2012) is used. Moreover, since it has been proven that differences in QRS location and RR time series measured from different ECG leads are strongly linked to breathing (García-González et al. 2014), all computations presented in this study are obtained using the same ECG lead, namely lead II.

The mean of the RR intervals, and the normalized power for each segment were computed. The power spectrum was computed using the Lomb-Scargle periodogram, and the frequency bands for the power computation were set as:

- Low frequency band (LF): $0.04\text{Hz} \leq \text{LF} < 0.15\text{Hz}$
- High frequency band (HF): $0.15\text{Hz} \leq \text{HF} < 0.4\text{Hz}$.

The power values were normalized to the sum of the total power in LF and HF. After that, the respiratory signals were filtered using a high-pass Butterworth filter with cutoff frequency at 0.05Hz, in order to remove baseline wander. Finally, the tachogram and the respiratory signals were normalized to zero mean and unit variance.

In the remaining of this document the RR interval time series will be denoted by RR, and the EDR signals by Res.

2.3. Information dynamics

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

$$P_{\mathbf{Y}} = H(Y_n) - H(Y_n|\mathbf{X}_n^-, \mathbf{Y}_n^-), \tag{1}$$

where the first term corresponds to the *Shannon entropy* of Y_n, and the second term refers to the *conditional entropy* of Y_n knowing the past of both variables in the process. If the contribution to Y_n from the past of only one particular variable needs to be retrieved, the definition in (1) can be rewritten as

$$P_{\mathbf{Y}} = H(Y_n) - H(Y_n|\mathbf{Y}_n^-) + H(Y_n|\mathbf{Y}_n^-) - H(Y_n|\mathbf{X}_n^-, \mathbf{Y}_n^-), \tag{2}$$

where the term $H(Y_n) - H(Y_n|\mathbf{Y}_n^-)$ refers to the *self-entropy* $S_{\mathbf{Y}}$ ((Lizier et al. 2012)), which corresponds to the amount of information carried by Y_n, that can be predicted by its own past. In other words, $S_{\mathbf{Y}}$ can be seen as the information storage of $\mathbf{Y}$. Large values of $S_{\mathbf{Y}}$ indicate that there is a high predictability of the heart rate. However, no distinction between the information coming solely from heart rate and the information transferred from respiration can be made. The second term quantifies the amount of information transferred from $\mathbf{X}_n^-$ to Y_n, and that cannot be predicted from $\mathbf{Y}_n^-$. This corresponds to the *transfer entropy*, $T_{X\to Y}$ ((Schreiber 2000)).

The expression in (1) can alternatively be written as

$$P_{\mathbf{Y}} = H(Y_n) - H(Y_n|\mathbf{X}_n^-) + H(Y_n|\mathbf{X}_n^-) - H(Y_n|\mathbf{X}_n^-, \mathbf{Y}_n^-), \tag{3}$$

where the predictive information is defined as the sum of the *cross-entropy* $C_{X\to Y}$ and the *conditional self entropy* $S_{Y|X}$ (Faes & Porta 2014). $C_{X\to Y}$ quantifies the amount of information shared between Y_n and the past of $\mathbf{X}$. When there is a large amount of

information transferred from the respiration to the heart rate, one expects this value to be also large. $S_{Y|X}$ corresponds to the residual amount of information that can be retrieved from the past of $\mathbf{Y}$. 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 using the decomposition in (3) is that it is possible to split the information carried by heart rate into two components: respiration and others (e.g. sympathetic activation).

The computation of $S_{\mathbf{Y}}$, $T_{X\to Y}$, $C_{X\to Y}$ and $S_{Y|X}$ is done using the approach presented in Faes, Widjaja, Van Huffel & Nollo (2014) and Faes, Nollo, Jurysta & Marinazzo (2014), which makes use of the link between information theory and predictability. This procedure assumes that the process $\mathbf{U}$ has a joint Gaussian distribution. Under this assumption it is possible to describe the dynamics of $\mathbf{U}$ using a linear vector autoregressive (VAR) model of order p‡. This description of $\mathbf{U}$ allows to relate the conditional entropy terms to the error probabilities of a regression model. For instance, to compute $H(Y_n|\mathbf{X}_n^-)$, a regression of Y_n on $\mathbf{X}_n^-$ is performed and the residuals are used to compute the prediction error variance, which is then used to obtain the entropy term. Here, the prediction error variance is expressed in terms of variances and covariances matrices as described in Faes, Widjaja, Van Huffel & Nollo (2014) and Faes, Nollo, Jurysta & Marinazzo (2014). This procedure leads to an exact computation of the different entropy terms when the condition of Gaussianity is fulfilled. However, when this is not the case, the results are still valid, but they correspond to an approximation where only the linear part of the process is modeled. For details on the whole procedure, see Faes, Widjaja, Van Huffel & Nollo (2014) and Faes, Nollo, Jurysta & Marinazzo (2014).

The main reason to select this approach based on information dynamics is that it allows to quantify the amount of information actively stored in the heart rate and the amount of information transferred from respiration to heart rate. This is one of the most important advantages of this method over more classical approaches such as coherence, since the concept of causality and directionality in the interactions can be exploited. However, frequency domain methods that extend the coherence towards an assessment of directional interactions (e.g., directed transfer function and partial directed coherence) can be seen as an alternative. Nonetheless, in this study the approach based on information dynamics is preferred for two reasons: first, it allows a nice decomposition of the overall predictability into the storage and transfer components, which is not straightforwardly guaranteed by frequency domain methods; second, it takes the whole causal influences from driver to target (i.e., from respiration to heart rate) into account, while a frequency domain method limiting the analysis to the conventional HF band may miss influences occurring outside of this band.

‡ In this particular study, the order p is selected using the Akaike Information Criterion (AIC).

It is important to mention that the entropy measures described above are extensions of the concepts of mutual information (MI) and conditional MI to the analysis of the "dynamic" information shared between the present of the target variable (i.e., heart rate) and its past and that of the other variable (in this case, respiration). Originally, measures of MI can quantify only "static" information shared between variables. However, the extension leading to the formulation of information dynamics, allows to use MI measures for assessing temporal flows of information, making them applicable in the context of time series analysis where the temporal information is essential to capture dynamic interactions.

2.4. Statistical analysis

The methodology used in this work, not only allows the computation of the entropy terms using the covariance matrix, but also brings the possibility to evaluate the significance of the different terms (Faes, Nollo, Jurysta & Marinazzo 2014). This is done using F-statistics, where two linear regressions are compared, namely, the restricted linear regression and the unrestricted one, where Y_n is predicted from $\mathbf{Y}_n^-$ with the residual sum of squares indicated by RSS_r, and where Y_n is predicted from $[\mathbf{X}_n^-\mathbf{Y}_n^-]$ with RSS_u, respectively. The prediction errors produced by both regressions are compared and used to perform the test statistic defined as $F = ((RSS_r - RSS_u)/p)/(RSS_u/(N - nc))$, where N is the length of the predicted time series and nc the coefficients for the unrestricted model. A given entropy term is considered statistical significant if its corresponding F is larger than the critical value of the Fisher distribution with $(p, N - nc)$ degrees of freedom, and a significant level $\alpha = 0.05$.

On the other hand, the differences between the entropy estimates of different groups (AE, TLE and CO) were evaluated using the Kruskal-Wallis test, which is a non-parametric version of the one-way ANOVA, with 95% of confidence. Since three groups were analyzed, a multi-comparison test was used with Bonferroni correction equal to $\alpha/3$, with $\alpha = 0.05$.

3. RESULTS

Once the RR interval time series RR, and the respiratory signal Res were derived from each ECG segment of 5 minutes, time and frequency domain features were computed. Fig. 2 shows the comparison of the mean RR and the normalized power in the low and high frequency bands, between the three groups under study.

It is clear from Fig. 2 that the heart rate of patients suffering from AE is significantly higher than the one of control subjects. Remember that the figure shows the RR intervals which is inverse to the heart rate. These results were already reported in Varon et al. (2012) and Jansen et al. (2013), where several segments of one minute were used to make the comparison between AE and CO. Here, however, segments of 5 minutes were studied, and variations due to circadian rhythm were reduced due to

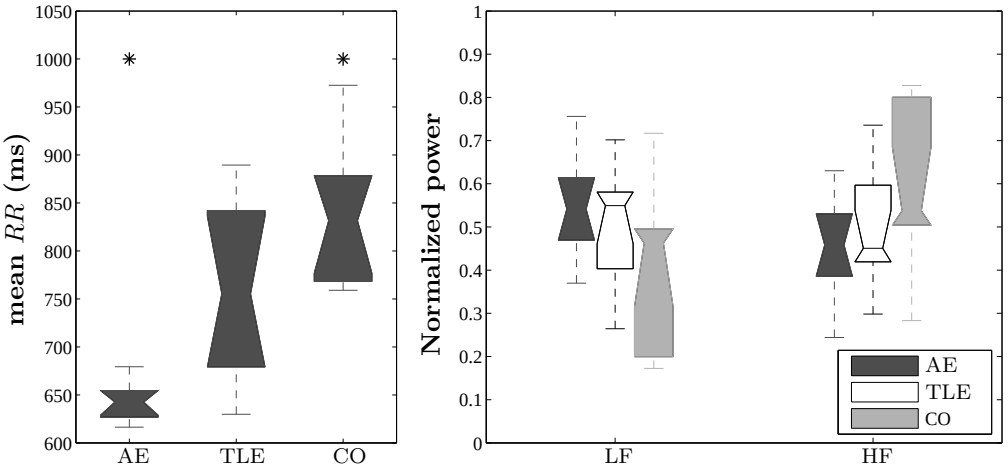


Figure 2. Parameters derived from the RR interval time series (RR). Significant differences ($p < 0.05$) are indicated by *. Note that the mean RR is significantly lower (higher heart rate) for patients suffering from AE than for the control subjects. The frequency domain parameters were normalized to the sum of the total power in the low (LF) and high (HF) frequency bands. The LF band was taken from 0.04Hz to 0.15Hz, and the HF band from 0.15Hz to 0.4Hz.

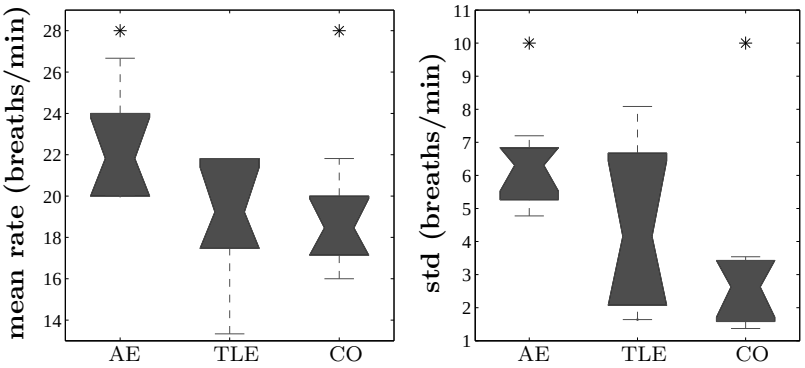


Figure 3. Mean and standard deviation of the respiratory rate computed from the EDR signals (Res). Significant differences ($p < 0.05$) are indicated by *. Note that the mean respiratory rate and the variability for patients with AE is significantly higher than for CO patients, which suggests an increased sympathetic modulation.

the fact that the selected segments correspond to the same time of the day (from 13h to 15h). In addition, the patients were awake and at ease on their beds, which also reduces the influences of the body position on the heart rate and respiration. Fig. 2 also shows the frequency domain parameters of RR, where it is possible to observe that the power in the low frequency band is higher, although not significantly, in AE than in CO. This might be an indication that a higher sympathetic modulation is taking place in AE patients. This is also observed when looking at Fig. 3, which shows the mean and the standard deviation of the respiratory rates. It is clear from the figure that the variability of the respiratory rate is significantly higher in AE when compared to control subjects.

The crucial point made so far is that the differences in RR and Res between CO

and patients suffering from AE, were also found in the segments under investigation. The next step is to look at the interactions between both physiological signals, and determine if epilepsy also has a profound effect on how these mechanisms interact with each other.

Fig. 4 shows entropy values for each group (AE, TLE and CO). Using the F-test described in the previous section, it was found that for all patients, the values of $S_{\mathbf{Y}}$, $C_{X\to Y}$ and $S_{Y|X}$ were significant, while values of $T_{X\to Y}$ were significant for 29 patients, with 9/10 control subjects. Remember that two decompositions of $P_{\mathbf{Y}}$ were used: $S_{\mathbf{Y}}+T_{X\to Y}$ and $C_{X\to Y}+S_{Y|X}$. As can be seen from the figure, the only significant differences were obtained between AE and CO concerning the values for cross-entropy ($C_{X\to Y}$) and conditional self entropy ($S_{Y|X}$).

When looking at the predictive information, it is observed that heart rate variability is predicted slightly better in normal subjects than in patients with epilepsy. However, no significant differences were found. Therefore, it is very interesting to look at the different entropy terms in both decompositions described in section 2. The first term corresponds to the self entropy $S_{\mathbf{Y}}$, for which only a slight trend towards higher information storage of RR in the control group is observed. Before drawing conclusions about the predictability of the heart rate in normal subjects, it is useful to look at the conditional self entropy $S_{Y|X}$. The latter quantifies the information stored in the heart rate, without taking into account information transferred from the respiration. In other words, $S_{Y|X}$ looks at mechanisms, different from respiration, that affect the heart rate (e.g. sympathetic activation). For this entropy term, it is observed that in control cases, there is less information shared between the heart rate and its past, which implies that the heart rate is less predictable and more adaptable, thereby allowing a faster reaction on acute changes. This effect is more pronounced in the AE group, which also confirms that there is an interictal autonomic alteration in this kind of patients.

Turning now to the amount of information transferred from respiration to heart rate, it is necessary to look at the transfer entropy $T_{X\to Y}$, and the cross-entropy $C_{X\to Y}$. Fig. 4 also indicates that more information is shared between RR and Res in CO than in AE. TLE is in between both groups. This can be seen from both entropy terms, but the difference is statistically significant only for the cross-entropy. The higher sensitivity of the cross-entropy compared to the transfer entropy can be explained by the fact that the latter, in the presence of unidirectional interactions like those presumably existing from respiration to heart rate, tends to underestimate the information transfer (Faes, Widjaja, Van Huffel & Nollo (2014)). The significantly smaller information transfer measured by the cross-entropy in AE compared with CO suggests that the influence of respiration on the HR is also changed during AE, which confirms that not only respiration itself is altered in this type of epilepsy.

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 reported in Jansen et al. (2013) and O'Regan & Brown (2005).

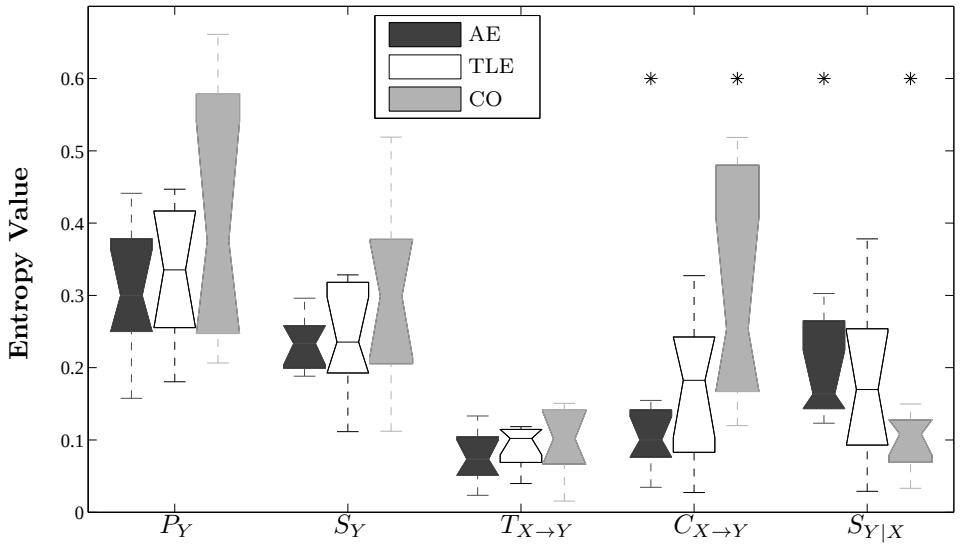


Figure 4. Boxplots of predictive information P_Y, self-entropy S_Y, transfer entropy $T_{X\to Y}$, cross-entropy $C_{X\to Y}$, and conditional self entropy $S_{Y|X}$ for the three groups: absence epilepsy (AE), temporal lobe epilepsy (TLE) and control group (CO). Note that the second decomposition corresponding to $C_{X\to Y} + S_{Y|X}$, allows to find significant differences ($p < 0.05$, indicated by *****) between AE and CO. This is an indication of an increased autonomic dysfunction in AE. TLE displays a less severe alteration to the autonomic controls, and it resembles better the properties of the control group.

4. DISCUSSION

Prior studies have shown that when looking at interictal data of children suffering from epilepsy, physiological parameters like heart rate, respiration (Jansen et al. 2013, Varon et al. 2012) and heart rate variability (Harnod et al. 2008) are significantly affected. In children with refractory epilepsy, the HRV is significantly lower, which can be explained by a reduced vagal activity. These observations were also clear in this study, where it was shown that patients with absence epilepsy (AE) present a reduced/increased parasympathetic/sympathetic modulation during seizure-free activity, in comparison to the control group. This was clear from the values of conditional self entropy that indicate a less flexible heart rate in AE, which can be seen as a predisposition of these patients to experience life-threatening episodes that can led to sudden death. In Billman & Hoskins (1989), Harnod et al. (2008), it was discussed that an increase sympathetic activity may cause a reduction in the thresholds for life-threatening tachycardias or bradycardias. This is a crucial point that needs to be taken into account when diagnosing children suffering from epilepsy, especially those suffering from AE.

Knowing that the heart rate and respiration are both affected in epilepsy, it is now crucial to also take into account their interactions, especially in AE. Two main points were observed here:

(i) the information going from respiration to heart rate is significantly lower in AE

than in CO,

(ii) and the heart rate in AE is highly predictable, which might indicate an increased sympathetic, and decreased parasympathetic activation.

On the other hand, no significant differences were found between TLE and CO. However, it is well known that these seizures are accompanied by bradycardia or tachycardia (Singh et al. 2013), and most of the times by apnea episodes (Blumhardt et al. 1986). Then again, this seems to occur during ictal activity in this type of epilepsy. Hence, the focus is now on interictal changes observed in AE.

It is known that in AE the thalamocortical network, which connects the thalamus and the cerebral cortex, has an important role in the generation of epileptic discharges (Gigout et al. 2013). Studies in rats have shown that the effectiveness of the synaptic responses in this network is lower in rats with AE. Furthermore, there exist differences in the connectivity of this network when compared to controls. These two observations are very important, because the respiratory centers of the brain get input from brain systems like the thalamus, prefrontal cortex, amygdale and insula (Pattinson et al. 2009). Hence, it is possible to think that the thalamocortical network could be more sensitive to changes in AE, causing a long term alteration to the respiratory control mechanism. In this way, the interactions between respiration and heart rate might also be affected, which can result in a dysfunctional regulation of central nervous functions, like arousal. This is of course a hypothesis that needs to be confirmed in further studies.

5. CONCLUSIONS

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