Time, frequency and information domain analysis of short-term heart rate variability during pre- and post-ictal periods in epileptic children

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Abstract

Objective: Epilepsy produces strong effects on heart rate variability (HRV), which have been investigated exhaustively with time- and frequency-domain indexes during seizure activity, but to a lesser extent using information-theoretic descriptors and during interictal (seizure-free) activity. In this work we explore the potential of novel information measures, combined with standard indexes, for the characterization of pre-ictal and post-ictal HRV in epileptic children.
Approach: we analyze short-term HRV in 42 children suffering from generalized or focal epilepsy, monitored 10s, 300s, 600s and 1800s both before and after repeated seizure episodes. For each patient and epoch, six HRV indexes are computed in the time (mean, root mean square of the successive differences), frequency (low-to-high frequency power ratio LF/HF and HF central frequency) and information (conditional entropy and self entropy) domains.
Main results: We find that the early post-ictal phase is characterized by significant tachycardia, depressed HRV, shift of the sympatho-vagal balance and decreased HRV complexity, which are progressively recovered across time windows after the episodes. These results are overall more peculiar of focal than generalized seizures.
Significance: Our analysis helps in elucidating the pathophysiology of interictal autonomic control of HRV and the differential diagnosis of generalized and focal epilepsy. These findings may also have clinical relevance since altered sympathovagal control can be related to a higher danger of morbidity and mortality, may cause a reduction in thresholds for life-threatening arrhythmias, and could be a biomarker of risk for sudden unexpected death in epilepsy.

Keywords: focal epilepsy, generalized epilepsy, Heart Rate Variability, complexity

1. Introduction

Epilepsy is a brain disorder with recurrent and unpredictable interruptions of normal brain function (Fisher *et al* 2005). Such events are defined *epileptic seizures* and consist in transient synchronous or abnormally excessive brain activity (Fisher *et al* 2005). Seizures are usually classified into two main types, i.e. *focal* that are generated within networks limited to one hemisphere, and *generalized seizures* which instead rapidly involve bilaterally distributed networks in the whole brain, often even causing loss of consciousness (Berg *et al* 2010, Varon *et al* 2015). Epilepsy is a chronic disease relatively widespread, with estimated incidence and prevalence of 6.38 and 0.68 per 1000 persons, respectively, according to a recent study (Fiest *et al* 2017). The incidence of epilepsy is higher in the youngest and oldest people and is also slightly higher in males than in females (Fiest *et al* 2017).

According to a recent classification, there are three different main causes that may provoke the onset of epilepsy: (i) genetic factors, (ii) structural or metabolic condition or disease (e.g., brain injury, tumor, stroke, trauma, infection), (iii) unknown origins, when epileptic seizures are a consequence of a separate but not yet unrecognized disorder (Berg *et al* 2010). Epilepsy produces cognitive, psychological and social consequences (Fisher *et al* 2005) and can significantly impair quality of life, due to the frequent and unpredictable seizures, cognitive deficits, comorbid mood and psychiatric disorders (Devinsky *et al* 2018). Symptoms are really various, strictly depending on the site of the epileptic discharges (Varon *et al* 2015). The main manifestations of epileptic seizures usually consist in convulsions, trembling, jerking, rapid contraction/extension of the muscles, stiffening, loss of awareness, a sensation of déjà vu or even a smell of burnt rubber (Devinsky *et al* 2018, Varon *et al* 2015). In worst cases, sudden unexpected death in epilepsy (SUDEP) can occur, with an estimated incidence of ~1 in 1,000 adults with epilepsy (Devinsky *et al* 2018, Sveinsson *et al* 2017) due to the inability to recover after an epileptic seizure.

One of the most used diagnostic techniques for clinical diagnosis of epilepsy is electroencephalography (EEG). EEG analysis should be carried out in patients in case of an apparent first unprovoked seizure or suspected epilepsy, and can help differentiating epileptic seizures from non-epileptic events, classifying seizure type (e.g., focal or generalized) or even predicting the risk of seizure recurrence (Smith 2005, Devinsky *et al* 2018). Although EEG is relatively noninvasive and accurate, other techniques are underway investigated for daily monitoring of epileptic patients and for seizure prediction. In particular, recent research works have highlighted that monitoring heart rate variability (HRV) in epileptic subjects could be also of interest (Myers *et al* 2018). This is because it is well known that epilepsy has a deep effect on the autonomic nervous system (ANS), especially on the ANS control of HRV (Myers *et al* 2018, Jansen and Lagae 2010, Varon *et al* 2015, Devinsky 2004, Harnod *et al* 2008). HRV represents a noteworthy measure for assessing cardiac health as well as the ANS status, being able to reflect cardiovascular complexity and the organism capability to react to environmental and psychological stimuli (Shaffer and Ginsberg 2017, Acharya *et al* 2007, Agrò *et al* 2014, Evans *et al* 2013). Potentialities of HRV have nowadays increased also thanks to more widespread availability of minimally invasive and portable or even wearable devices which can be employed for real-time assessment of physiological parameters (Hernando *et al* 2018, Bánhalmi *et al* 2018, Oreggia *et al* 2015, Vinciguerra *et al* 2019). In epileptic patients, HRV can be evaluated between seizures (*interictal*), during seizures (*ictal*), before seizures (*preictal*), after seizures (*postictal*), or over a long period (e.g., 24 hours) which may or may not include seizures (Myers *et al* 2018). Previous findings have highlighted that patients with epilepsy usually show tachycardia that can precede, coincide or follow ictal discharges, while bradycardia and bradyarrhythmia are much less frequent (Jansen and Lagae 2010, Leutmezer *et al* 2003, Opherk *et al* 2002).

The study of HRV over short periods of time can open a noninvasive window on the physiological mechanisms underlying the establishment of an epileptic seizure in the pre-ictal phase and the recovery of normal ANS function in the post-ictal phase. Short-term HRV is usually assessed from electrocardiographic (ECG) recordings computing the time intervals between subsequent heartbeats of (i.e., the RR intervals, *RRI*) and considering sequences of 300 beats (about 5 minutes) (Shaffer and Ginsberg 2017, Malik *et al* 1996). Short-term HRV analysis is a viable tool to evaluate changes in the ANS activity related to altered psycho-physiological states (Shaffer and Ginsberg 2017, Taelman *et al* 2011, Porta *et al* 2007, Pernice *et al* 2019, 2018). This analysis is commonly performed in the time domain computing measures like the mean and variance of RRI sequences, as well as the Root Mean Square of the Successive Differences (*RMSSD*), which reflects vagally mediated changes in HRV (Shaffer and Ginsberg 2017); *RMSSD* is more influenced by the parasympathetic nervous system (PNS) than standard deviation (Shaffer and Ginsberg 2017). Moreover, frequency-domain HRV indexes play an important role to study the autonomic nervous function of the organism (Shaffer and Ginsberg 2017, Karemaker 2017). In particular, the power content of HRV in the low- and high-frequency bands (LF, 0.03-0.15 Hz; HF, 0.15-0.4 Hz) have been long used as measures of sympathetic and parasympathetic ANS tones, so that the *LF/HF* power ratio has been employed to describe the balance between

sympathetic and parasympathetic activities (Shaffer and Ginsberg 2017, Karemaker 2017). However, the reliability of *LF/HF ratio* as a measure of the autonomic balance is a matter of debate, as recent outcomes have shown that an increased activity in one system does not necessarily imply a decreased activity in the other one in any condition (Draghici and Taylor 2016, Shaffer and Ginsberg 2017, Karemaker 2017). In relation to this issue, recent developments in time series analysis have made it possible to complement the information provided by time- and frequency-domain indexes with measures derived from the field of information theory (Porta *et al* 2001, Faes *et al* 2017, Voss *et al* 2009, Humeau-Heurtier 2015). In particular, measures like the conditional entropy (Porta 1998) and information storage (Lizier *et al* 2012) – reflecting respectively complexity and regularity of the investigated time series, have been shown to reflect accurately the degree of involvement of the sympathetic branch of the ANS in a variety of physiological states and pathological conditions (Porta *et al* 2017, Faes *et al* 2013, Al-Angari and Sahakian 2007).

From the above discussion, it is evident that HRV has a great potential in clinical applications for monitoring the ANS status in epileptic patients, supporting the robust classification among interictal, preictal and postictal states, and also serving as a biomarker for SUDEP. However, the research in this direction has been limited up to now by the lack of consistently used protocols, as only recently a minimum protocol for HRV evaluation to be used for epileptic patients has been proposed, which is based exclusively on *RMSSD* (Myers *et al* 2018). It is nevertheless evident that an accurate assessment of ANS control for different types of epilepsy and in the different phases of seizure episodes can be possible only monitoring a wide range of HRV measures providing thorough and complementary information. For this reason, the present work aims at exploring the potential of time-domain, frequency-domain and information-theoretic measures for the characterization of short-term HRV in epileptic subjects studied in the pre-ictal and post-ictal phases of generalized and focal seizure episodes. The comprehensive analysis carried out in this work could be exploited to select the most important HRV features for epileptic patients.

2. Materials and methods

2.1 Subjects and Experimental Protocol

This study considers forty-two patient children (22 males, 20 females, age: 6.63±5.20 years), admitted at the TMO "Psychiatry" clinic of Kyiv (Ukraine). Patients were suffering from focal seizures (26 children) or from generalized seizures (16 children), diagnosed according to common clinical and electroencephalographic criteria (Smirnov *et al* 2017). Antiepileptic drugs were administered in therapeutic dosages to the patients based on their diagnosis: patients with focal epilepsy were treated with carbamazepine, lamotrigine, lacosamide, topiramate, valproic acid; patients with generalized epilepsy were on valproic acid, lamotrigine, topiramate, and vigabatrin.

In these patients, ECG data were collected during a total of 81 generalized and 99 focal seizures. In order to characterize the progression towards each episode and the departure from it, HRV was measured over short sequences (300 samples) of the RR interval in eight different windows, located 30 min, 10 min, 5 min and 10 s both before (preictal) and after (postictal) the seizure event. In the following, preictal time windows will be indicated in the figures as "PRE", while postictal as "POST".

2.2 Time series and data analysis

RR intervals were extracted from the ECG using custom technique based on a modified Pan-Tompkins method (Pan and Tompkins 1985). In order to take into account incorrect detections and arrhythmic heart beats, time series were filtered according to the procedure described in (Popov *et al* 2017, Wichterle *et al* 2004). In detail, an iterative procedure was applied to remove RR intervals different more than 25% from the interpolated mean of immediately preceding and following values (Popov *et al* 2017).

For each RR sequence, time domain analysis was performed taking the average value (*MEAN*) and the Root Mean Square of the Successive Differences, calculated as follows (Vollmer 2015):

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{n=1}^{N-1}(x(n+1)-x(n))^2}\,, \qquad (1)$$

where $x(n)$ represents the n-th measurement of the RRI interval and N=300 is the time series length.

Before carrying out frequency and information domain analyses, the time series were pre-processed removing slow trends, followed by subtraction of the mean value. Then, spectral analysis was performed employing the weighted covariance method to obtain the spectrum of each time series. In detail, the Blackman-Tukey method for spectral analysis (see, e.g., Pinna *et al* 1996) was applied by FFT-transforming (512 points) the windowed sample autocovariance of RRI data, using the Parzen spectral window with bandwidth B_w=0.04 Hz and setting the truncation point M of the corresponding lag as follows:

$$M = \frac{1.273F_S}{B_W}\,, \qquad (2)$$

being F_s the reciprocal of the mean RR interval length. Figure 1 depicts an example of RRI time series (a) and of the corresponding power spectrum (b). From the spectrum, the power in the low frequency band (LF, 0.04-0.15 Hz) and in the high frequency band (HF, 0.15-0.4 Hz) were extracted, and the low-to-high frequency power ratio (*LF/HF*) was

computed (Shaffer and Ginsberg 2017, Malik *et al* 1996). Moreover, the frequency of the most prominent peak located in the HF band (f_{HF}) was detected and interpreted as an indication of the respiration related oscillatory activity in the HRV (Shaffer and Ginsberg 2017).

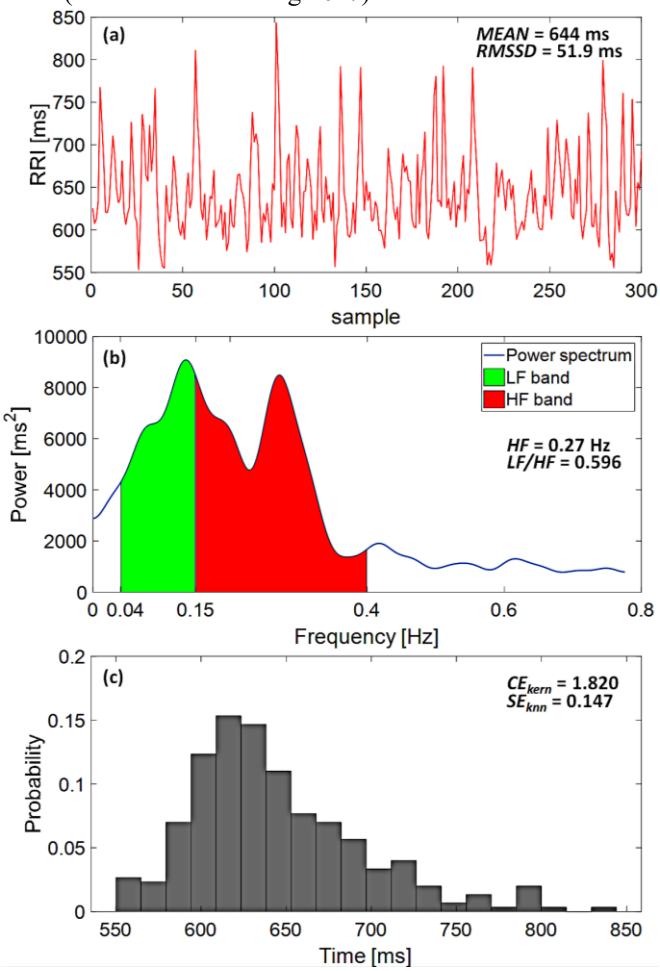

Figure 1. Representative example of a RRI time series measured after an epileptic seizure (a), together with its corresponding power spectral density (b) and probability distribution (c). The values of time, frequency and information domain indexes computed from this exemplary time series are shown in the three panels.

Information domain analysis was performed computing the amounts of new information (conditional entropy, *CE*) and of information storage (self entropy, *SE*) relevant to short-term HRV (Richman and Moorman 2000, Porta *et al* 1998, Xiong *et al* 2017). For a generic time series x, self entropy is the part of the entropy of the present sample $x(n)$ that can be derived from the past samples $x(n-1),\ldots, x(n-m)$, while conditional entropy is instead the residual information contained in $x(n)$ but not in the past samples $x(n-1),\ldots, x(n-m)$. Conditional entropy and self entropy can be defined as statistical functions of the probability distributions of the present and past samples as follows (Xiong *et al* 2017):

$$C_X = -E\left[log\frac{p(x(n),x(n-1),\ldots,x(n-m))}{p(x(n-1),\ldots,x(n-m))}\right] \quad (3)$$

$$S_X = E\left[log\frac{p(x(n),x(n-1),\ldots,x(n-m))}{p(x(n))\cdot p(x(n-1),\ldots,x(n-m))}\right] \quad (4)$$

An example of the probability distribution $p(x(n))$, estimated for an RRI time series using histogram quantization, is reported in Figure 1(c). In this work, the information indexes defined in Eqs. (3) and (4) were calculated using the two most popular model-free approaches for their estimation, i.e., the kernel estimator of the *CE* which returns the well-known Sample Entropy (Richman and Moorman 2000) and the k-nearest-neighbor estimator of the *SE* which guarantees bias compensation (Faes *et al* 2015); we refer also to (Xiong *et al* 2017, Valente *et al* 2018, Pernice *et al* 2019) for further detailed information. In particular, the kernel estimate of *CE* (CE_{kern}) was obtained with threshold distance parameter r=0.2, while the k-nearest-neighbor estimate of *SE* (SE_{knn}) was obtained using k=10 neighbors; the embedding dimension (number of past lags) was set to m=2 for both estimators.

2.3 Statistical analysis

The analyses carried out in this work were aimed at comparing HRV indexes in eight different time windows, located 1800 s, 600 s, 300 s and 10 s both before (preictal) and after (postictal) the seizure event, for both focal and generalized seizures. Specifically, our focus was on the assessment of differences between the period immediately preceding (or immediately following) the epileptic discharge and the periods more far away from the episode.

Accordingly, for each time-, frequency- and information domain index, statistical analysis was performed as follows. First, an individual value of the index was obtained, for each patient and pre- or post-ictal window, computing the median of the index over the several seizures manifested for the patient in the analyzed window. Then, the distribution across patients of the index computed in the time window nearest to the epileptic seizure (10 s) was compared to that of all the other time windows (either PRE or POST). Moreover, pairwise comparisons were also performed, for any assigned time window, between pre- and post-ictal phases. In both cases, the statistical significance of the differences between distributions was assessed using the non-parametric Wilcoxon paired signed rank test.

After performing the analysis above described grouping together all subjects, statistical tests were repeated analyzing separately patients with focal seizures and patients with generalized seizures. In this second analysis, differences between windows given the phase, and between pre-ictal and post-ictal phases given the window, were performed as before; in addition, the statistical significance of the differences between focal and generalized distributions of an

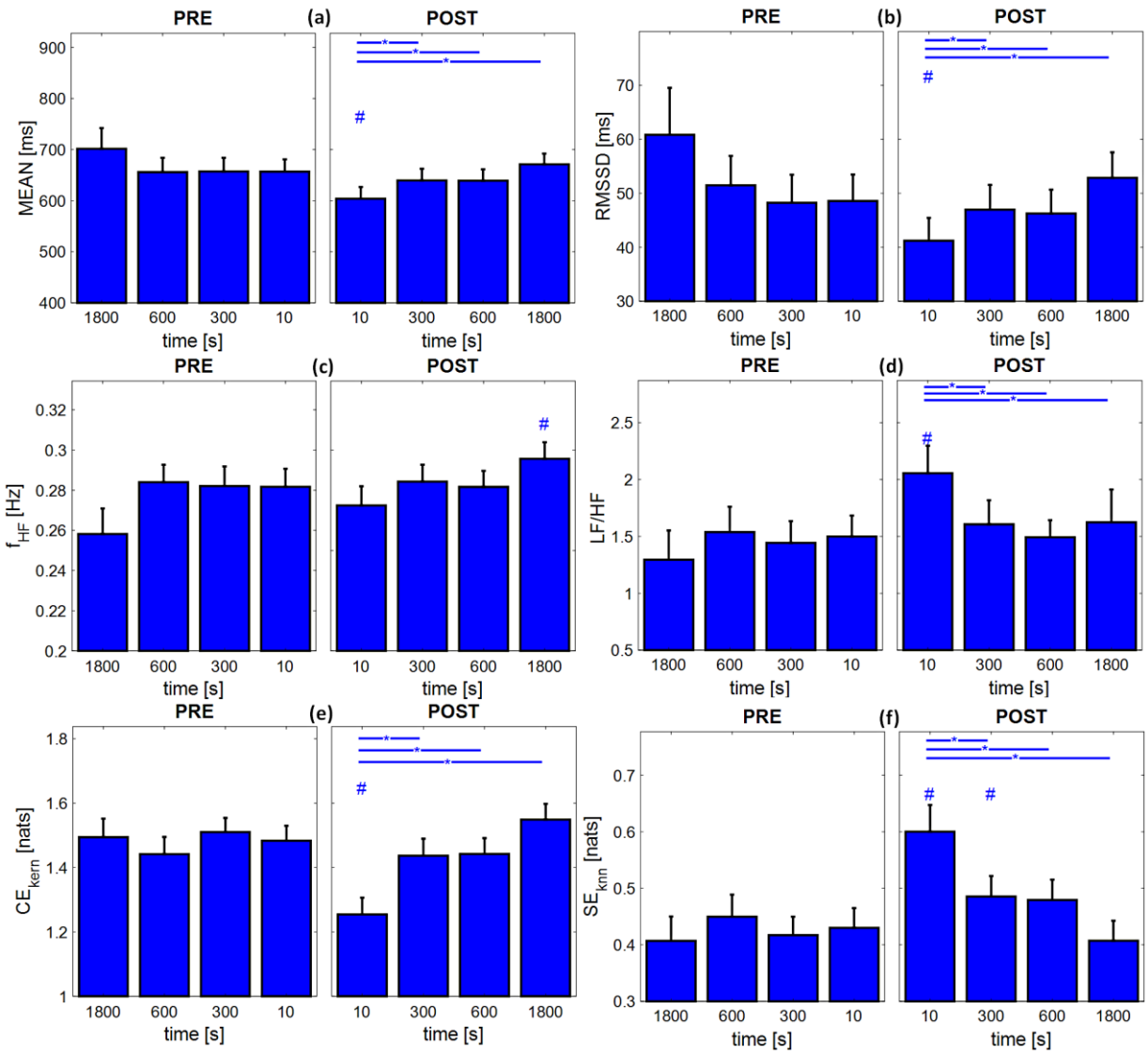

Figure 2. Distributions of HRV indexes, i.e., (a) *MEAN*, (b) *RMSSD*, (c) f_{HF}, (d) *LF/HF*, (e) CE_{kern}, (f) SE_{knn} calculated taking into account all seizures (both focal and generalized), for the eight considered time windows (1800, 600, 300, 10 s, both pre- and post-ictal). Statistical tests: #, p<0.05 PRE vs POST; *, p<0.05 first (10 s) window vs other window.

index was assessed, for each assigned phase and time window, using the Wilcoxon unpaired rank sum test.

In all tests, the null hypothesis of equal median across patients was rejected considering a *p*-value < 0.05 as statistically significant.

3. Results

Figure 2 shows the comparison of the distributions of all the HRV indexes across the 42 subjects in the eight different time windows (1800 s, 600 s, 300 s and 10 s either PRE or POST). In each bar plot, bars represent the mean value of the index in the time window taken into account, while whiskers denote the standard error.

The analysis of *MEAN* distributions (Fig. 2(a)) showed a non-statistically significant decrease of the average value of RRI from 1800 s to 10 s before the seizure (from 700 to around 650 ms). *MEAN* value of RRI resulted significantly lower just after the seizure compared to the pre-ictal phase (~600 ms vs. ~650 ms, 10 s POST vs. 10 s PRE), and then increased significantly, gradually recovering to almost the starting value. During the pre-ictal phase, *RMSSD* decreases from 60 to around 48 ms (non-significant change), while a stronger and statistically significant reduction was observed just after the seizure (p<0.05 10 s POST vs. 10 s PRE). The values of *RMSSD* at 10 s POST were significantly lower than the other POST distributions.

The frequency of the most prominent peak located in the HF band (f_{HF}), shown in Fig. 2(c), did not vary significantly neither during the PRE phases nor during the POST phases, ranging between ~0.26 Hz and ~0.29 Hz; the only significant difference was that between the PRE and POST distributions at 1800 s. The *LF/HF* ratio (shown in Fig. 2(d)) did not vary significantly across the preictal windows, maintaining average values slightly lower than 1.5. Instead, a strong surge of this index was observed just after the seizure. The *LF/HF* ratio then decreased while moving away from the episode, returning to the values observed before the seizure (the decrease was statistically significant for all post-ictal phases).

The conditional entropy computed using the kernel estimator did not show any substantial variations during the pre-ictal phases (Fig. 2(e)), while a strong statistically significant decrease was observed just after the seizure (10s POST). Afterwards, CE_{kern} increased gradually up to the starting values, the difference being statistically significant for all windows. The self-entropy assessed with the k-nearest-neighbor method showed opposite trends, being almost constant during the pre-ictal phase, exhibiting a strong increase just after the epileptic seizure (10 s POST), and returning gradually to the preictal values afterwards. The 10 s distribution of SE_{knn} resulted statistically different from all the following, while the comparison of PRE vs POST distributions showed this time a statistical difference not only at 10 s, but also at 300 s.

Figure 3 shows the comparison of the distributions of all the HRV indexes considering separately the focal seizure group (26 patients) and the generalized seizure group (16 subjects). As reported in the figure, the trends in terms of increase or decrease of the various indexes appear similar to that described in Fig. 2 for the overall distributions. With regards to *MEAN* (Fig. 3(a)), the values were significantly lower for the generalized seizure group if compared to the focal seizure group (600s, 300s and 10s PRE, 10s and 1800s

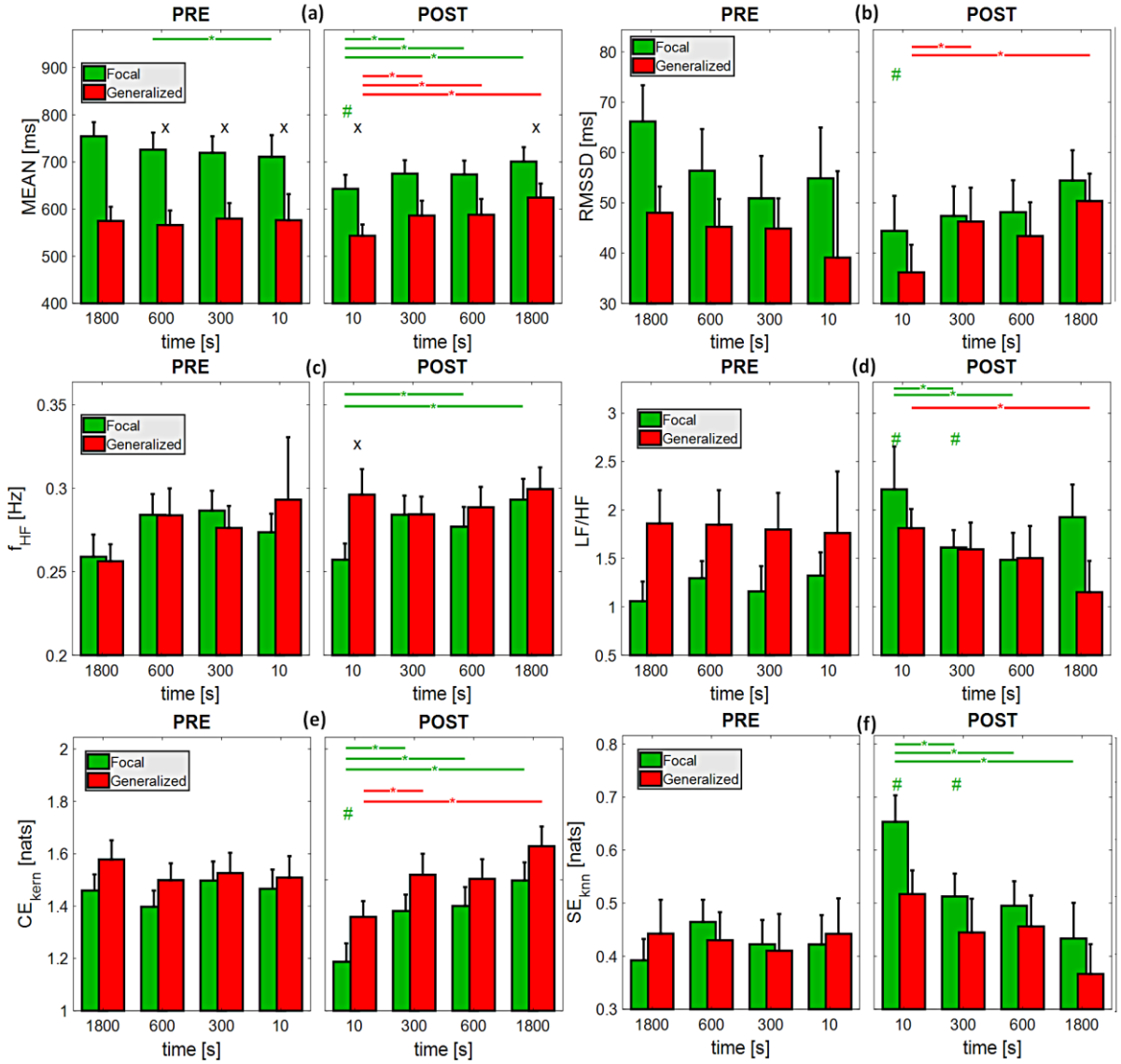

Figure 3. Comparison of focal and generalized distributions of HRV indexes, i.e., (a) *MEAN*, (b) *RMSSD*, (c) f_{HF}, (d) *LF/HF*, (e) CE_{kern}, (f) SE_{knn}, for the eight considered time windows (1800, 600, 300 and 10 s, both pre- and post-ictal). Statistical tests: #, $p<0.05$ PRE vs POST; *, $p<0.05$ 10s window vs other window; X, focal vs generalized. Green symbols refer to focal seizures, while red symbols to generalized seizures.

POST windows; Fig. 3(a)). The opposite behavior was observed for the LF/HF ratio (Fig. 3(d)), but it was limited to the pre-ictal phase and was not statistically significant. The 10s post-ictal values of the respiration-related HRV rhythm, f_{HF}, were significantly higher during generalized seizures (Fig. 3(c)). In the other cases, the average values of focal and generalized seizures distributions are comparable.

Statistical tests for the individual groups reported trends similar to those previously described for the whole population, with the observation that overall more differences between distributions are reported in the case of focal seizures. In particular, the 10s POST focal distribution was reported as significantly different from all other POST distributions for the *MEAN*, CE_{kern} and SE_{knn} indexes; with regard to *LF/HF* ratio, the 10s POST focal distribution was statistically different from two POST distributions (600s and 1800s). Interestingly, the 10s POST values of f_{HF} were significantly lower than the 600s and 1800s (Fig. 3(c)), showing a behavior that was not reported for the whole population. With regard to PRE versus POST comparison, the distributions at 10 s have been reported statistically different in all the cases, apart from f_{HF}. In case of LF/HF ratio and SE_{knn}, also the PRE / POST distributions at 300s resulted statistically different.

Fewer differences were instead reported in the case of generalized seizures (red bars and symbols). In particular, the 10s POST distribution was different from all the other POST distributions only for the *MEAN* index; the 10s POST distribution was different from 1800s POST also for *RMSSD*, *LF/HF* ratio and CE_{kern}; and from 300s POST also for *RMSSD* and CE_{kern}. A statistical difference was found also between the 10s and 600s PRE distributions of *MEAN* in the preictal phase (Fig. 3a). No differences were found for the SE index during POST (Fig. 3f). No statistically significant differences were found between the PRE and POST distributions for the group of generalized seizures. An opposite behavior, not documented for the overall population nor for the group with focal seizures, was observed for *RMSSD* during the postictal phases, which showed in the patients with generalized seizures a statistically significant increase comparing the 10s distribution with the 300s and 1800s distributions.

4. Discussion

Time domain analysis shows, in the early period just after the seizure, significantly lower values of *MEAN*, and its progressive recovery across windows (Figs. 2(a) and 3(a)). This behavior documents the occurrence of tachycardia, likely induced during the seizure and still remarkable after its termination. This is in agreement with the literature, as ictal tachycardia has been reported in 86.9% to up to 100% of seizures (Eggleston *et al* 2014, Leutmezer *et al* 2003, Opherk *et al* 2002). Analyzing the changes in the mean heart rate according to the type of seizure (Fig. 3(a)), we observe that post-ictal tachycardia and its progressive recovery are evident for both generalized and focal epilepsy. A main difference between the two groups is that children with generalized seizures are more tachycardic, even in the pre-ictal phase. Thus, it seems that the involvement of large scale brain structures in epilepsy has a bigger impact on the changes in the heart rate associated with seizures, as also reported in previous studies where ictal tachycardia was found significantly higher during, or immediately after, generalized than non-generalized seizures (Devinsky *et al* 2018)(Devinsky 2004, Opherk *et al* 2002). Moreover our results show, only for children with focal seizures, a tendency to the anticipation of tachycardia in the pre-ictal phase, documented by the statistically significant decrease of *MEAN* from 10 min to 10 sec before the seizure (Fig. 3a). This result is in line with previous findings documenting pre-ictal heart rate increases (see (Eggleston *et al* 2014) for a review), even though its validity in terms of seizure prediction is limited by the large time window adopted in this study (300 sec).

In addition to the reduced mean RRI, our results demonstrate a decrease of *RMSSD* just after the event, with statistically different 10 s POST and PRE distributions (Figs. 2(b) and 3(b)). In agreement with previous reports (Myers *et al* 2018, Jansen and Lagae 2010, Surges *et al* 2010), such results indicate a reduction in the short-term components of HRV following epileptic seizures, likely related to a decreased parasympathetic ANS modulation. This finding has clinical relevance, as depressed vagal tone can make patients more vulnerable to tachycardia and fibrillation and, in worst cases, to SUDEP (Jansen and Lagae 2010). In particular, it has been demonstrated that reduced *RMSSD* values can be correlated with higher scores on a risk inventory of SUDEP in (DeGiorgio *et al* 2010, Shaffer and Ginsberg 2017). The comparison between the two types of seizures documents that RMSSD during the early post-ictal phase is reduced in comparison with the pre-ictal phases for focal seizures, and in comparison with the following post-ictal phases for generalized seizures. Moreover, the overall reduced *RMSSD* observed for generalized seizures confirms previous observations (Surges *et al* 2010) reporting lower post-ictal HRV for generalized tonic-clonic seizures than for complex partial seizures.

The frequency of the most prominent peak located in the HF band did not show noteworthy variations across phases when computed for the overall population. On the other hand, the comparison between the two groups evidenced a significantly lower HF frequency during the first post-ictal phase in the patients suffering from focal seizures, with a frequency that was also reduced if compared to the following time windows (Fig. 3c). This peculiar finding is indicative of significant variations in the breathing rate that could be

associated with the respiratory abnormalities reported for epileptic patients in (O'Regan and Brown 2005). Specifically, defining *tachypnoea* (*bradypnoea*) as a 10% increase (decrease) in respiratory rate from the median value recorded in a baseline condition far away in time from seizure episodes (in our case, at 1800s PRE), tachypnoea is present during all post-ictal phases for generalized seizures and only for the 300 s and 1800 s post-ictal phases for focal seizures. This relates to the work of (O'Regan and Brown 2005) who found that tachypnoea was the predominant response for generalized seizures (in over 90% of the seizures), while it was less predominant in case of focal seizures (60% of the seizures).

The *LF/HF* power ratio exhibited a strong surge in the post-ictal phase just after the epileptic seizure and was recovered to basal values in the following phases (Fig. 2(d)). This denotes a lower vagal activity and/or higher sympathetic activity just after the seizure, and thus can be interpreted as an indication of a shift in autonomic balance towards sympathetic dominance. This trend reflects other findings previously reported in the literature (Myers *et al* 2018, Lotufo *et al* 2012, Evrengül *et al* 2005, Kolsal *et al* 2014, Jansen and Lagae 2010, Surges *et al* 2010) and, given that lower vagal and higher sympathetic activity are predictors of morbidity and mortality in ANS dysfunctions, could eventually be an important clinical biomarker for risk for SUDEP (Myers *et al* 2018, Lotufo *et al* 2012). The differences between post-ictal and preictal phases is particularly evident for subjects suffering from focal seizures (Fig. 3(d)), and may reflect in these patients the occurrence of long-term postictal disturbances of the ANS regulation. Protracted effects of an unbalanced *LF/HF* ratio towards sympathetic activity in the post-ictal phase have been observed already, even up to 5-6 hours (Toth *et al* 2010).

Like most of the indexes computed in the time and frequency domain, also the information-theoretic measures did not vary significantly during the pre-ictal phases (Fig. 2(e)), and this trend was observed similarly considering the individual seizure groups (Fig. 3(e)). Instead, just after the seizure (10 s POST) a strong decrease is observed for the conditional entropy (Fig. 2(e)) together with a strong increase in the self entropy (Fig. 2(f)). The new information produced by HRV (conditional entropy) was progressively recovered, and the information stored in HRV (self entropy) gradually diminished, across time windows after the episodes. The diminished capability to produce new information and the increased capability to store information can be taken as an indication of the decreased complexity and increased regularity of the cardiac dynamics (Porta *et al* 2001, Faes *et al* 2017). Given that these indexes have been related to different degrees of involvement of the sympathetic nervous system in a variety of physiopathological states (Porta *et al* 1998, 2001, 2007, 2017, Faes *et al* 2013, Valente *et al* 2018), the decreased conditional entropy and increased information storage are likely reflecting a sympathetic overactivity that characterizes the early post-ictal phase, which takes several minutes to recover to interictal values. Noticeably, these results were found more prominently during focal than during generalized episodes, suggesting that post-ictal sympathetic alterations related to epilepsy are more profound when the seizure onset is localized in space within the brain. Our information-theoretic results are consistent with a study of HRV carried out on children suffering either from temporal lobe epilepsy (characterized by seizures with *mild* manifestations) or absence epilepsy (characterized by generalized seizures causing impairment of consciousness) reporting a reduced parasympathetic and an increased sympathetic modulation during time intervals between seizures (Varon *et al* 2015).

A limitation of the present study lies in the fact the analyzed children were treated with antiepileptic drugs at the time of measurement. As these drugs may alter autonomic regulation, we cannot exclude that part of the observed changes, or lack thereof, can be due to the effects of medications and of their interaction with epilepsy. Since it has been reported that variations of HRV time domain parameters are blunted in medicated epileptic patients than in untreated ones (Hallioglu *et al* 2008), it is possible that some of the autonomic impairments observed in this study could be more marked in the absence of treatment, and some of the changes not observed (e.g., in the pre-ictal phases) may be related to the improvement brought to the autonomic function by the treatment. Finally, we underline as another possible limitation that in our study seizure epochs have not been taken into account, being often noisy and also short or anyway lacking of stable electrocardiographic traces long enough to obtain reliable HRV estimates.

5. Conclusion

Our results provide evidence that epilepsy in the children is associated with changes in the autonomic function affecting the post-ictal sympathetic and parasympathetic nervous system activities, which are noticeable for several minutes after the termination of epileptic seizures. These changes are associated with a shift of the sympatho-vagal balance towards elevated sympathetic activity and depressed parasympathetic activity, and are followed by a slow progressive recovery of the balance to interictal values. The utilization of novel information-theoretic measures complementing the values of standard time and frequency domain indexes allowed to point out more clearly the state of sympathetic overactivity manifested in the post-ictal phases. Overall, the observed results were more evident in focal than in generalized epilepsy; this suggests that the related autonomic effects, possibly including sympathetic and respiratory centers, are peculiar of seizure manifestations

involving localized areas of the brain. Our findings may have clinical relevance as elevated sympathetic activity may cause a reduction in the thresholds for life-threatening arrhythmias.

Future work should extend these investigations to ictal periods (Eggleston *et al* 2014), and should be directed to study organ system interactions involving combined analyses of HRV and of cardiovascular, cardiorespiratory and brain signals monitored in epileptic subjects (Schiecke *et al* 2016, Pereda *et al* 2005). This would allow to elucidate the role of physiological mechanisms like the respiratory sinus arrhythmia or the baroreflex on the ANS regulation during epilepsy, as well as to disambiguate the 'peripheral' effects manifested in the ANS dynamic control of heart rate from the central neural pathways producing the cortical brain rhythms.

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