

Analysis of Brain-Heart Interactions in newborns with and without seizures using the Convergent Cross Mapping approach*

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Abstract— In the last years, the characterization of Brain-Heart Interactions (BHIs) in epilepsy has gained great interest. For some specific seizures, there is still a lack of information about the mechanisms that occur during or close to ictal events between the Central Nervous System (CNS) and the Autonomic Nervous System (ANS). That is the case for neonatal seizures, one of the most common neurological emergencies in the first days of life. This paper evaluated possible differences in BHIs between newborns with seizures and seizure-free ones. We applied Convergent Cross Mapping approaches to a cohort of 52 newborns from a public dataset. Even though preliminary, results showed that newborns with seizures have a lower degree of interaction between the CNS and the ANS than the seizure-free ones (Mann-Whitney test: p -value < 0.05). These results are of clinical relevance for future studies about using BHI approaches to better understand the neural mechanisms behind neonatal seizures.

Clinical Relevance— The study of BHIs in newborns with seizures might be helpful to better characterize the disorder or the aetiologies behind ictal events. Moreover, BHI approaches may confirm the involvement of the ANS during or close to a neonatal seizure event.

I. INTRODUCTION

It is well known that a mutual exchange of information exists between the cortical activity of the Central Nervous System (CNS) and the Autonomic Nervous System (ANS). For example, cardiac activity can be altered by inputs from baroreceptors, chemoreceptors, and other sources [1]. Thus, the analysis and the characterization of the Brain-Heart interactions (BHIs) during physiological and pathological events is of great clinical interest [1]. The ANS-to-CNS system interaction was investigated and modelled using physiological signals such as the electroencephalogram (EEG) and the Heart Rate Variability (HRV) [1, 2]. Moreover, several methodologies were proposed to measure or model these interactions, such as Granger Causality, Transfer Entropy and the Convergent Cross Mapping (CCM) [2]. Above mentioned methods have been applied in various neuroscience applications such as polysomnography [3], mood disorders or emotion recognition [4] and epilepsy [5, 6]. In particular, the study of BHI in epilepsy could have strong implications for

diagnosis and therapy to detect signs or symptoms related to a sudden unexpected death in epilepsy (SUDEP) [6].

However, there is still a lack of information about the interactions between CNS and ANS during or close to several seizure events [6], such as neonatal seizures, the most common neurological emergency in the first days of life of the newborn [7]. According to a recent ILAE position paper [7], neonatal seizures deserve a particular classification among seizure events, both for the intrinsic electroclinical characteristics of the newborn (when compared to the adult [8]), and their aetiologies [9]. Seizure detection is tricky and time-consuming, and delayed treatment can negatively affect neurodevelopment [7, 10]. The analysis of interactions between physiological systems has already been performed for newborns, mainly to assess neurovascular coupling [11, 12]. However, to the best of our knowledge, a specific investigation of BHIs in newborns with seizure events using EEG and HRV signals is still scarce [11]. As stated in [13], there is increasing evidence about a significant involvement of ANS during neonatal seizures. Similarly to the “epileptic heart” in the adult and the child [14], it seems that neonatal seizures might have a direct/indirect involvement on heart dynamics as well as on the ANS. In particular, the Central Autonomic Network (CAN) might have an active role in the seizure onset [7, 13, 15]. This study investigated BHIs in newborns with and without seizures using EEG and HRV signals. The aim is to assess if different behaviors may exist between the CNS and ANS for the two populations considered. We used the Convergent Cross Mapping method (CCM) [16], already adopted for the analysis of BHI in specific childhood epilepsy [5]. Proposed methods were developed and validated on a public dataset of neonatal EEG and ECG signals recorded in the Neonatal Intensive Care Unit (NICU) at the Helsinki University Hospital, Helsinki, Finland [17].

This paper is organized as follows: Section II describes the dataset used, the pre-processing applied to EEG and ECG signals and the BHIs analysis performed with CCM. In Section III, statistical results are shown. Section IV is devoted to the discussion about the use of BHI for the characterization of newborns with seizure events and seizure-free ones. Conclusions are drawn in Section V.

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II. MATERIAL AND METHODS

The proposed methods were implemented under the MATLAB computing environment (version 2021b [18]). We developed our methods using a public dataset of EEG and ECG signals collected at Helsinki University Hospital, Helsinki, Finland [17]. Signals were recorded with the NicoletOne System, Natus Medical [17], with a sampling frequency of 256Hz. Seventy-nine newborns were independently evaluated by three experts, labelling the time occurrence of the seizure events (labels' frequency: 1Hz). 39 patients had a unanimous consensus about seizure presence inside the recordings. For 22 patients, the experts did not find any seizures, and we considered them seizure-free patients. In this study, we analyzed only the patients with unanimous consensus [19, 20]. Thus, the remaining 18 patients were excluded. Moreover, 9 patients were excluded as their ECG signal was not present or was highly corrupted by noise. Therefore, our analysis was applied to 33 patients with seizure events and 19 seizure-free ones. We used the same bipolar configuration for EEG analysis as in [19, 21]: F4-C4, C4-O2, F3-C3, C3-O1, T4-C4, C4-Cz, Cz-C3 and C3-T3.

All the EEG signals were filtered with a band-pass FIR filter in the bandwidth 0.25-16 Hz. ECG signals were analyzed to extract HRV time series. Both ECG and EEG underwent a sub-windowing procedure of 30s of duration [5, 21]. Specifically, ECGs were first pass-band filtered, in the bandwidth of 0.05-45 Hz, to increase the Signal-to-Noise Ratio (SNR). Then Inter-Beat-Interval (IBI) time series were obtained through the Pan-Tompkins' algorithm [21, 22]. Eventually, the HRV signals were interpolated to have the same number of samples of the EEG signals. We checked the following interpolation methods in this preliminary evaluation: linear, nearest neighbour and the French-Holden algorithm [2, 5]. Moreover, both EEG and the interpolated HRV were downsampled to 16 Hz, obtaining 480 samples in each window.

For each EEG derivation and each 30s window, we evaluated the CCM correlation coefficients between the EEG and the HRV signals. The CCM approach is a nonlinear method to assess causality between two time series X and Y, observing the correspondence between the so-called "Shadow Manifolds" M_X and M_Y , built using lagged coordinates from the original time series X and Y [2, 16]. The lagged versions depend on the following parameters: the embedding dimension D, the time lag τ and the library length L [2, 5, 16]. In our case, L was equal to the number of window's samples (L=480). Following the indications in [2, 5], we investigated values for D from 2 to 8 and for τ from 1 to 5.

The interactions between the two systems were quantified by CCM correlation, defined as the absolute value of the Pearson correlation coefficient (ρ) between the original time series and an estimation using the CCM with the other time series [2, 5]. In other words, we obtained, for all the 8 derivations considered, two CCM indexes (1) and (2) defined as follows:

$$CCM_{EEG \rightarrow HRV} = |\rho(EEG, EEG|M_{HRV})| \quad (1)$$

$$CCM_{HRV \rightarrow EEG} = |\rho(HRV, HRV|M_{EEG})| \quad (2)$$

CCM implementation details can be found in [23]. Moreover, we computed the Average Degree metrics [12] as the mean of CCM values, both for (1) and (2), between all the derivations considered.

A. Statistical Analysis

We computed the overall mean of CCM coefficients for each patient, distinguishing between seizure events and seizure-free patients. First, we tested if CCM values (1) and (2) and the Average Degree's CCM values were statistically different between the two groups. The hypothesis of normality distribution was checked through the Shapiro-Wilk test (level of significance $\alpha=0.05$). As the normality hypothesis was not confirmed, we applied the non-parametric Mann-Whitney test (Test MW, level of significance $\alpha=0.05$).

Moreover, we added a surrogate analysis to verify if the CCM values were not due to chance or random fluctuations within the time series but represent a specific interaction between the two systems. To this aim, for each window, we built a set of 100 surrogates from the HRV interpolated signal using the Amplitude-Adjusted Fourier Transform (AAFT) method [24]. Then for the surrogate sets, we computed the CCM correlation coefficients (1) and (2) and the Average Degree. We considered a CCM value as significant if it was greater than the following significance thresholds: $T_{surr} = \mu_{surr} + 2\sigma_{surr}$; where μ_{surr} and σ_{surr} are the mean and the standard deviation values of the metrics obtained from the surrogate sets [25]. Furthermore, to test statistical differences between surrogates' CCM values and CCM values from the original time series, we applied a non-parametric Mann-Whitney test (level of significance $\alpha=0.05$).

III. RESULTS

In Table I, the statistical results obtained on $CCM_{EEG \rightarrow HRV}$ mean values between 33 patients with seizure events and 19 seizure-free patients are shown. The same analysis for the Average Degree parameter is reported in the last row.

TABLE I. RESULTS OF STATISTICAL TESTS FOR THE PARAMETER $CCM_{EEG \rightarrow HRV}$ PERFORMED BETWEEN EACH DERIVATION AND HRV SIGNAL. THE DESCRIPTIVE STATISTICS (MEAN $\mu \pm$ STANDARD DEVIATION σ) ARE SHOWN. STAR (*) DENOTES STATISTICALLY SIGNIFICANT RESULTS.

Derivation	CCM EEG \rightarrow HRV		Test MW
	Seizure-free patients $\mu \pm \sigma$	Patients with seizures $\mu \pm \sigma$	p-value
F4-C4	0.23 \pm 0.08	0.18 \pm 0.05	0.010*
C4-O2	0.24 \pm 0.07	0.19 \pm 0.06	0.001*
F3-C3	0.22 \pm 0.10	0.18 \pm 0.07	0.106
C3-O1	0.22 \pm 0.07	0.19 \pm 0.09	0.154
T4-C4	0.24 \pm 0.08	0.19 \pm 0.06	0.020*
C4-Cz	0.25 \pm 0.07	0.19 \pm 0.06	0.012*
Cz-C3	0.23 \pm 0.08	0.19 \pm 0.08	0.018*
C3-T3	0.21 \pm 0.10	0.18 \pm 0.09	0.223
Average Degree	0.23 \pm 0.08	0.20 \pm 0.07	0.029*

The descriptive statistics are related to the following CCM's parameters: D=3, $\tau=1$, L=480. The interpolation method selected for this experiment was the linear one. The same statistical analysis related to $CCM_{HRV \rightarrow EEG}$ is shown in Table II. Table III concerns the descriptive statistics of CCM parameters related to surrogate analysis. We reported the

average significant thresholds and their standard deviations for patients with seizure events and seizure-free patients. Star (*) denotes a statistically significant difference with the CCM values computed with the original time series. To assess statistical differences, we used a non-parametric Mann-Whitney test (level of significance $\alpha=0.05$).

TABLE II. RESULTS OF STATISTICAL TESTS FOR $CCM_{HRV \rightarrow EEG}$. THE DESCRIPTIVE STATISTICS (MEAN $\mu \pm$ STANDARD DEVIATION σ) ARE SHOWN. STAR (*) DENOTES STATISTICALLY SIGNIFICANT RESULTS.

Derivation	CCM HRV \rightarrow EEG		Test MW
	Seizure-free patients $\mu \pm \sigma$	Patients with seizures $\mu \pm \sigma$	p-value
F4-C4	0.11 \pm 0.03	0.11 \pm 0.04	0.530
C4-O2	0.10 \pm 0.03	0.10 \pm 0.05	0.287
F3-C3	0.12 \pm 0.04	0.10 \pm 0.04	0.493
C3-O1	0.09 \pm 0.03	0.10 \pm 0.03	0.044*
T4-C4	0.10 \pm 0.02	0.11 \pm 0.05	0.071
C4-Cz	0.11 \pm 0.02	0.11 \pm 0.03	0.196
Cz-C3	0.10 \pm 0.03	0.11 \pm 0.04	0.371
C3-T3	0.09 \pm 0.02	0.10 \pm 0.03	0.019*
Average Degree	0.10 \pm 0.02	0.11 \pm 0.04	0.183

TABLE III. DESCRIPTIVE STATISTICS (MEAN $\mu \pm$ STANDARD DEVIATION σ), FROM SURROGATE ANALYSIS. STAR (*) DENOTES SIGNIFICANT DIFFERENCES BETWEEN SURROGATES' CCM VALUES AND THEIR RESPECTIVE VALUES SHOWN IN TABLE I AND II.

Derivation	Test Surrogates $T_{surr} = \mu_{surr} + 2\sigma_{surr}$			
	CCM EEG \rightarrow HRV		CCM HRV \rightarrow EEG	
	Seizure-free patients $T_{surr} (\mu \pm \sigma)$	Patients with seizures $T_{surr} (\mu \pm \sigma)$	Seizure-free patients $T_{surr} (\mu \pm \sigma)$	Patients with seizures $T_{surr} (\mu \pm \sigma)$
F4-C4	0.12 \pm 0.02*	0.10 \pm 0.02*	0.10 \pm 0.01	0.10 \pm 0.02
C4-O2	0.13 \pm 0.03*	0.11 \pm 0.03*	0.09 \pm 0.02	0.10 \pm 0.02
F3-C3	0.12 \pm 0.03*	0.10 \pm 0.02*	0.10 \pm 0.02	0.10 \pm 0.01
C3-O1	0.12 \pm 0.03*	0.11 \pm 0.02*	0.09 \pm 0.02	0.10 \pm 0.02
T4-C4	0.13 \pm 0.03*	0.12 \pm 0.03*	0.10 \pm 0.02	0.10 \pm 0.02
C4-Cz	0.14 \pm 0.03*	0.11 \pm 0.02*	0.10 \pm 0.01	0.10 \pm 0.01*
Cz-C3	0.13 \pm 0.03*	0.11 \pm 0.02*	0.10 \pm 0.02	0.10 \pm 0.02
C3-T3	0.12 \pm 0.03*	0.10 \pm 0.02*	0.09 \pm 0.02	0.10 \pm 0.02
Average Degree	0.12 \pm 0.03*	0.10 \pm 0.02*	0.09 \pm 0.01*	0.10 \pm 0.02

IV. DISCUSSION

This work evaluated whether CCM analysis could provide helpful and significant information about BHIs in newborns with and without seizures. As shown in Table I, we obtained significant results for $CCM_{EEG \rightarrow HRV}$ values for several derivations (5 out of the 8 considered) and for the Average Degree parameter (p -values < 0.05). Thus, the interaction between CNS and ANS may differ in patients with seizure events and seizure-free ones. Moreover, the average values of $CCM_{EEG \rightarrow HRV}$ were lower for patients with seizures than for seizure-free ones. This suggests that neonatal seizures might significantly alter the neuronal interplay between the two systems, making the ANS less "predictable" in response to variation of the CNS or cortical activity [5]. Low values of CCM mean a low causality relationship between two systems [2, 5]. We did not obtain significant results for all the derivations considered. That might be since neonatal seizures are mainly focal [7]. Thus, some cerebral areas may not be involved during ictal events for most patients in our dataset.

Since the surrogates' thresholds for $CCM_{EEG \rightarrow HRV}$ were lower than the original values (Table III and Table I, respectively), this result may confirm that these interactions may be due to specific relationships between CNS and ANS and not to random fluctuations of the time series. However, the same cannot be said about the $CCM_{HRV \rightarrow EEG}$ values: although we obtained significant results for two derivations (C3-O1 and C3-T3 in Table II), these results have to be considered with caution because the surrogates' values (Table III) did not show significant differences from them (p -value > 0.05). Thus, these interactions might be due to chance and not a real relationship between ANS and CNS. For example, Fig. 1a and 1b show the Average Degree's CCM trends of a single patient and their surrogates' analysis. As shown in Fig. 1a, the surrogates values remain below the $CCM_{EEG \rightarrow HRV}$, while $CCM_{HRV \rightarrow EEG}$ values remain lower than surrogates in almost all windows.

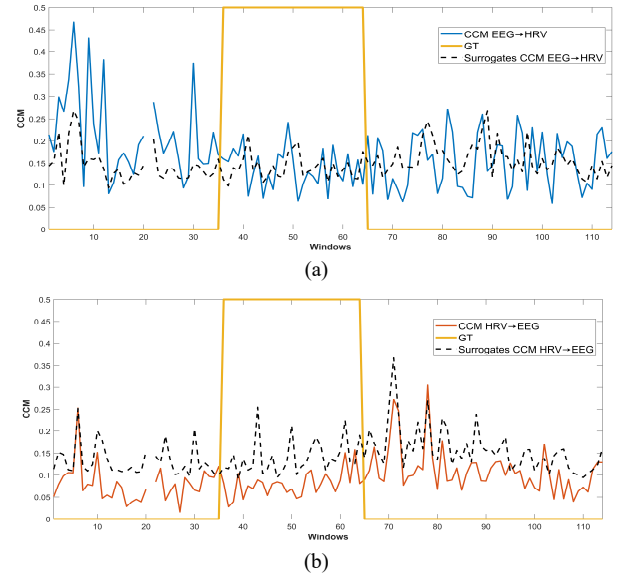


Figure 1. BHI analysis for a single patient with a single seizure event. (a) Average Degree's $CCM_{EEG \rightarrow HRV}$ trend (blue line) and the corresponding surrogates' values for each window (dashed line). (b) Average Degree's $CCM_{HRV \rightarrow EEG}$ trend (red line) and the corresponding surrogates' values for each window (dashed line). The orange line between windows 35 and 65 represents the time occurrence of the seizure event.

Thus, our results suggest that in patients with seizure events, the heart dynamics could be altered by the CNS activity but not the opposite. It agrees with [7, 9, 13]: seizures may alter the ANS dynamics and not only the CNS one. The CCM approach seems to catch differences in BHIs in newborns with and without seizures. However, our analysis has some limits. First, the choice of montage is a critical point, and it may alter the BHI results. Thus further analysis is needed to find which montage could be the best for neonatal BHI analysis. Anyway, as shown in Table I, multichannel analysis can provide better information than a single derivation analysis because some derivations may not conduct significant interactions. Another critical issue concerns the choice of CCM parameters D , τ and L , which could not be the best if used on other datasets. Thus, an exhaustive evaluation should be done when CCM analysis is applied to other datasets [5].

We confirmed that BHIs might differ in newborns with seizures and seizure-free ones. Future studies could focus on

intrinsic differences of BHI for patients with seizure events. They could focus on differences between interictal and ictal periods [20] or between pre-ictal and post-ictal periods [8]. Others could investigate BHIs among different aetiologies [7, 9]; or how BHI varies after pharmacological treatments [6].

V. CONCLUSIONS

Our results must be considered preliminary, and further studies are needed to confirm the usefulness of BHI in neonatal seizure detection and characterization. However, our findings suggest that ANS and HRV analysis are strictly related to seizure events in newborns. This information could better understand these pathological events and support neonatal seizure detection methods [9, 10, 19].

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