Complexity Modulation in functional Brain-Heart Interplay series driven by Emotional Stimuli: an early study using Fuzzy Entropy

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Abstract— **Increasing attention has recently been devoted to the multidisciplinary investigation of functional brain–heart interplay (BHI), which has provided meaningful insights in neuroscience and clinical domains including cardiology, neurology, clinical psychology, and psychiatry. While neural (brain) and heartbeat series show high nonlinear and complex dynamics, a complexity analysis on BHI series has not been performed yet. To this end, in this preliminary study, we investigate BHI complexity modulation in 17 healthy subjects undergoing a 3-minute resting state and emotional elicitation through standardized image slideshow. Electroencephalographic and heart rate variability series were the inputs of an ad-hoc BHI model, which provides directional (from-heart-to-brain and from-brain-to-heart) estimates at different frequency bands. A Fuzzy entropy analysis was performed channel-wise on the model output for the two experimental conditions. Results suggest that BHI complexity increases in the emotional elicitation phase with respect to a resting state, especially in the functional direction from the heart to the brain. We conclude that BHI complexity may be a viable computational tool to characterize neurophysiological and pathological states under different experimental conditions.**

I. Introduction

The anatomical and functional links between the central (CNS) and the autonomic nervous systems (ANS) define the so-called central autonomic network (CAN) [1], whose biochemical, electrical, and mechanical signalling have been comprehensively referred to brain-heart interplay (BHI). This functional and bidirectional interplay involves several cortical and subcortical areas, as well as cardiac sympathetic and parasympathetic activities that are deeply involved in affective regulation and perceptual and cognitive processing, among others [2].

The quantification of functional BHI may be performed through several computational tools, which have recently been categorized according to features including time-varying estimation, linearity, ad-hoc and physiologically-inspired modeling, and directionality [2]. For example, ad-hoc computational models [3], or general purpose signal processing methods [4], have been applied to quantify BHI, along with other directional [5] and non-directional estimations [6], time-resolved [7] or non-dynamical measures [8]. An interesting feature of BHI models refers to their ability to provide time-varying estimates. While such estimates may be useful to characterize the BHI evolution in time, group-wise statistics performed between different experimental populations and/or conditions usually take averaged measurements into account. Furthermore, although brain and cardiovascular series show high nonlinear and complex dynamics, and functional BHI extends to the multifractal domain [6], it is yet unknown whether BHI series show complex dynamics as well.

To this end, in this preliminary study we perform a Fuzzy Entropy (FuzzyEn) analysis on the output of the synthetic data generation model [9], which properly combines EEG and HRV series to provide directional BHI estimates at different frequency bands. FuzzyEn was chosen because of the provided advantages with respect to the more standard approximate and sample entropies, such as a low dependency on data length and robustness to noise [10].

FuzzyEn exploits fuzzy theory as embedded in the sample entropy algorithm [11], [12] and relies on the definition of fuzzy membership functions, which are a family of exponential functions providing a smooth boundary for similarity measures when compared to more rigid solutions (e.g., the Heavyside function). Such advantages require the definition and tuning of an extra parameter as the gradient of the fuzzy membership function boundary, along with the standard parameter set comprising the length of the time series, embedding dimension, and similarity tolerance.

Previous studies have investigated physiological complexity on EEG and HRV series through FuzzyEn in different experimental conditions [13], [14]. For example, an EEG study reported a complexity decrease over the central cortex and midline brain regions during motor imagery [13], and complexity in HRV series is statistically different between patients with heart failure and healthy controls [14].

In this preliminary study, BHI complexity is investigated through EEG and HRV series gathered from healthy subjects undergoing a resting state and an emotional elicitation session; such an elicitation was performed through standardized images gathered from the International Affective Picture System (IAPS) database [15]. The IAPS database [15] is a large collection of images associated with affective ratings expressed in terms of arousal and valence scores [16]. Arousal represents the perceived intensity of an emotion, and valence indicates how pleasant/unpleasant is the emotion.

Methodological details, as well as experimental results and

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conclusions follow below.

II. Materials and Methods

A. Experimental setup

Data from 17 healthy volunteers (10 women) aged from 21 to 28 were recruited after signing the study informed consent, which was approved by the Department of General Psychology Ethical Committee, University of Padua (Italy). The experimental protocol comprises a 3-minute resting state, during which subjects were seated on a comfortable chair in a silent, soundproof, and dark environment, followed by an emotional elicitation session. Such an elicitation was performed through a sequence of 72 IAPS images projected onto a screen. Every picture was shown for $0.6s$, and a blank interval (between $0.6s$ and $0.8s$) was posed in the middle of consecutive images. A group of images were chosen comprising pleasant, unpleasant, and neutral elicitation of several valence and arousal levels. Projected images were grouped in 18 blocks of 4 images, where each block comprised similar pictures (i.e., pleasant, unpleasant and neutral). Experimental data comprised EEG and ECG recordings sampled at $500Hz$. EEG series were gathered through a 32-channel Electro-Cap (Electrocap, Inc.) with thin electrodes placed according to the $10-20$ standard. The ECG was acquired using Ag/AgCl shallow electrodes placed on the subject's chest, following a modified lead II configuration. Subjects were asked to sit on a comfortable chair at a fixed distance of $70cm$ from the screen configured with maximum brightness.

B. Signal preprocessing

The EEG series were preprocessed using a semi-automatic pipeline, namely HAPPE [17]. First, the electrodes falling into the 1% external tails of the distribution derived by the average log-power normalized joint probability are marked as bad channels and rejected. Then, physiological, motor related, and electrical artifacts and discontinuities are detected and rejected by a cascade of a wavelet-enhanced independent component analysis (ICA)-based algorithm, followed by a fast-ICA and a machine learning algorithm [17]. Finally, bad channels previously rejected are interpolated through spherical approach, and the time-varying average from all electrodes was derived and used for re-referencing, as appropriate for a BHI study [18]. Regarding ECG series, an automatic algorithm has been used to identify R peaks [19]. Physiological and algorithmic artifacts were eventually corrected using Kubios HRV software.

Time-resolved power spectral density (PSD) was estimated on EEG series through short-time Fourier transform, with a Hamming window of 2000 samples (i.e., $2s$) and a 95% overlap, achieving PSD series sampled at $10Hz$. The PSD was then integrated in four classical EEG frequency bands: $\delta \in [1-4Hz)$, $\theta \in [4-8Hz)$, $\alpha \in [8-12Hz)$, and $\beta \in [12-30Hz)$. Time-resolved PSD on HRV series was estimated through the smoothed pseudo-Wigner–Ville distribution, which was integrated in the $0.04Hz$-$0.15Hz$ range for the low frequency (LF) band power and in the $0.15Hz$-$0.4Hz$ band for the high frequency (HF) band power. Both LF and HF power series were sampled at $10Hz$.

C. Brain-Heart Interplay estimation

The functional directional BHI was quantified through the synthetic data generation (SDG) model, fully described in [3], [9]. Briefly, the model embeds two coupled sets of equations, which may generate synthetic brain and heartbeat data. On the brain side, multiple oscillators generate synthetic EEG whose amplitude is modeled as an exogenous autoregressive model of the first order, and the exogenous term measures the heart-to-brain interplay [3]. On the heart side, an integral pulse frequency modulation model generates synthetic HRV series, and the embedded parameters are modulated by EEG activity and quantify the functional brain-to-heart interplay.

The SDG model is fitted on EEG power and HRV power series to provide time-varying BHI estimates throughout the HRV-LF and HF bands, and different EEG frequency ranges [2], [9]. Resulting BHI series have the same time resolution of PSD series, with a $10Hz$ sampling rate.

D. Fuzzy Entropy

Complexity in BHI series $u(i) : 1 \leq i \leq N$ from the SDG model was quantified through the FuzzyEn algorithm. To this end, the system phase space with a specific embedding dimension m has to be reconstructed. The distance d_{ij}^m between two vectors in the phase space is defined as:

$$d_{ij}^m = \max_{k\in(0,m-1)} \left\{ |u(i+k) - \mathbb{E}\left[u(i)\right] - (u(j+k) - \mathbb{E}\left[u(j)\right])| \right\} \tag{1}$$

where $(i, j = 1 : N-m, j \neq i)$, and $\mathbb{E}$ is the Expectation operator. The similarity degree D_{ij}^m is defined using the fuzzy membership function $\mu(d_{ij}^m, n, r)$, as shown in eq. 2:

$$D_{ij}^m = \mu(d_{ij}^m, n, r) = exp\left(\frac{-(d_{ij}^m)^n}{r}\right) \tag{2}$$

where n, r are the gradient of the boundary and the width of the exponential function, respectively. The FuzzyEn of a N-point time series can be defined as follows:

$$FuzzyEn(m, n, r, N) = \lim_{N\to\infty} [\ln \phi^m(n, r) - \ln \phi^{m+1}(n, r)] \tag{3}$$

where the function ϕ is:

$$\phi^m(n, r) = \frac{1}{N-m} \sum_{i=1}^{N-m} \left[\frac{1}{N-m-1} \sum_{j=1, j\neq i}^{N-m} D_{ij}^m \right] \tag{4}$$

The parameter r was set to $r = \rho \cdot SD$ according to [20], where ρ is the tolerance set to 0.2, and SD is the series standard deviation. The pseudo-optimal embedding dimension $m = 3$ was calculated by maximizing the probability that the estimate is valid [21]. FuzzyEn was calculated over BHI time series of 50 seconds (i.e. 500 samples), corresponding to the first $50s$ of resting state, and independently for each of the 4 blocks of emotional images.

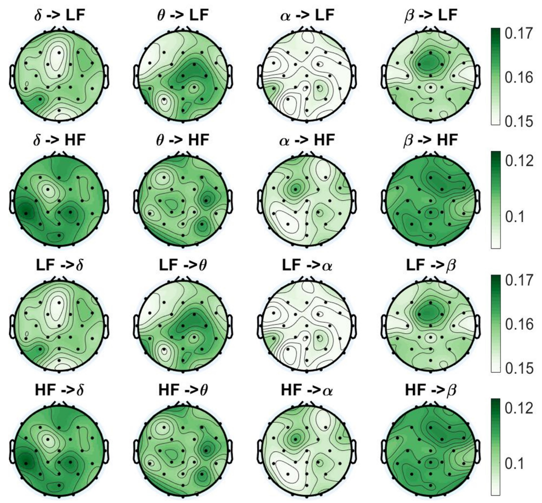

Fig. 1: Topographical representation of group-wise median of Fuzzy Entropy estimates from BHI time series during the resting state. Columns refer to EEG frequency bands (i.e., δ, θ, α, and β), top two rows refer to the brain-to-heart interplay in the HRV-LF and HRV-HF bands, and bottom rows refer to the heart-to-brain interplay in the HRV-LF and HRV-HF bands.

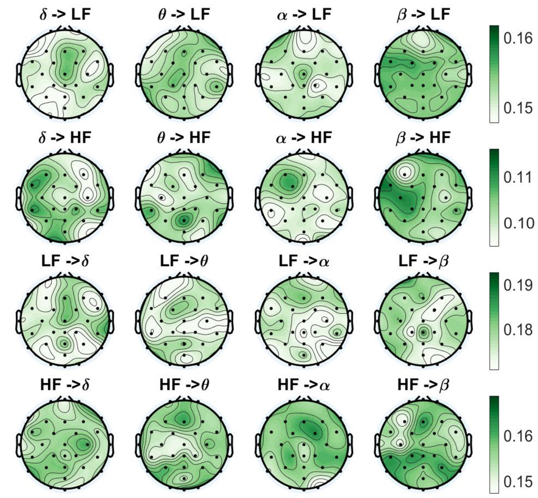

Fig. 2: Topographical representation of group-wise median of Fuzzy Entropy estimates from BHI time series during the emotional elicitation session. Columns refer to EEG frequency bands (i.e., δ, θ, α, and β), top two rows refer to the brain-to-heart interplay in the HRV-LF and HRV-HF bands, and bottom rows refer to the heart-to-brain interplay in the HRV-LF and HRV-HF bands.

E. Statistical analysis

Average FuzzyEn was calculated intra-subject between estimates of the 4 emotional image sessions, thus obtaining a single estimate for each subject for both the emotional elicitation and resting state sessions. In order to investigate differences in BHI complexity between the two experimental conditions (i.e., resting phase and emotional elicitation), a non-parametric Wilcoxon test for paired samples has been applied on FuzzyEn estimates for each EEG channel. To account for multiple comparison, a p-value correction was performed through a cluster-mass permutation correction, also assessing the physiological plausibility of the results [22].

III. Experimental Results

Descriptive results are reported as topographic maps, and Figures 1 and 2 show the group-wise median of FuzzyEn estimates in the resting state and emotional elicitation sessions, respectively. On both directions (from-brain-to-heart and from-heart-to-brain), BHI complexity seems higher when sustained by cardiac oscillations in the LF band with respect to the HF band. BHI series associated with EEG oscillations in the α band tend to show lower complexity with respect to the other frequency bands, especially in the resting state, whereas BHI series associated with EEG oscillations in the β band tend to show higher complexity.

Results from the statistical analysis are shown in Fig. 3 and highlight significant differences between the two experimental conditions, specifically in the heart-to-brain direction. In fact, while such an ascending direction shows diffuse scalp regions associated with statistical differences between sessions at every frequency band, no significant differences were found in the descending functional direction. Note that, in the heart-to-brain direction, the emotional elicitation session is associated with higher BHI complexity than resting state. Moreover, greater statistical difference is associated with cardiac vagal activity as estimated through HRV-HF power than the one of HRV-LF power.

IV. Discussion and Conclusions

While EEG and HRV complexity have extensively been studied in previous research, physiological complexity at a BHI level has not been properly assessed yet. To this end, we investigated functional BHI series complexity modulation in resting state and emotional elicitation sessions. BHI series for both heart-to-brain and brain-to-heart directions were gathered from an ad-hoc model combining EEG and HRV series [9], and BHI complexity was then quantified through FuzzyEn because of its robustness to noise and low sensitivity to parameter selection.

Results, referring to data from 17 healthy subjects, confirm that functional BHI series may be considered as the output of a nonlinear system whose complexity may be modulated by an emotional state induction. In particular, such a complexity modulation seems to occur in the heart-to-brain direction over non-specific brain regions and EEG frequency bands; a more significant effect seems to be associated with cardiac vagal activity, estimated through HRV-HF power. These findings are in line with previous emotional research studies reporting on a significant role of vagal activity (e.g., [23]), as well as heart-to-brain interplay [24].

As brain and cardiovascular systems show nonlinear and complex dynamics, complexity in BHI phenomena is not surprising and may reasonably be associated with the multiple feedback mechanisms occurring (but not limited to) at a hormonal, mechanical, and electrical levels between central

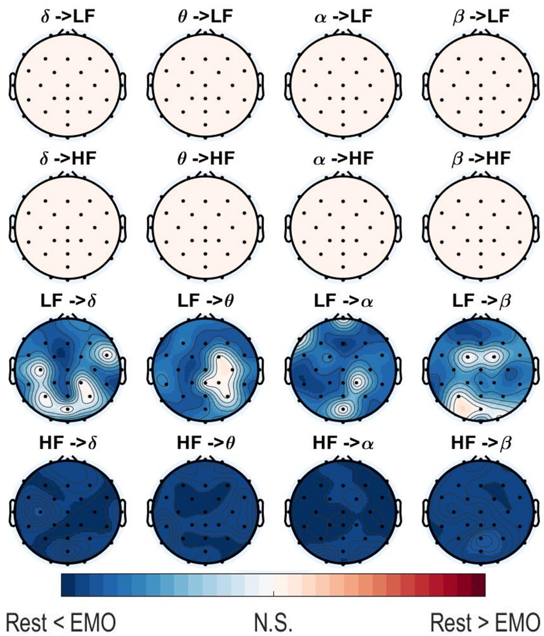

Fig. 3: p-value topographic maps for BHI complexity estimated through Fuzzy Entropy between resting phase (Rest) VS emotional elicitation (EMO) sessions. Columns refer to EEG frequency bands (i.e., δ, θ, α, and β), top two rows refer to the brain-to-heart interplay in the HRV-LF and HRV-HF bands, and bottom rows refer to the heart-to-brain interplay in the HRV-LF and HRV-HF bands.

and peripheral nervous systems. In this frame, we remark that functional BHI also extends to the multifractal domain [6].

Limitations of this study mainly refer to the relatively limited experimental data, and the use of a single functional BHI model and a single complexity quantifier. Future works will be directed to the application of the aforementioned computation to larger experimental datasets, also considering different pathophysiological and experimental conditions, together with the application of different BHI models.

Nonetheless, the present study provides meaningful insights on brain-heart neurophysiology and enrich the set of biomarkers that may be used for a dynamical characterization of the neural system as a whole.

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