Information-Theoretic Assessment of Cardiovascular-Brain Networks during Sleep

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Abstract

This study was aimed at detecting the structure of the physiological network underlying the regulation of the cardiovascular and brain systems during normal sleep. To this end, we measured from the polysomnographic recordings of 10 healthy subjects the normalized spectral power of heart rate variability in the high frequency band (HF) and the EEG power in the δ, θ, α, σ, and β bands. Then, the causal statistical dependencies within and between these six time series were assessed in terms of internal information (conditional self entropy, CSE) and information transfer (transfer entropy, TE) computed via a linear method exploiting multiple regression models and a nonlinear method combining nearest neighbour entropy estimation with dimensionality reduction. The statistical significance of CSE and TE was assessed using an F-test for the linear method, and an empirical randomization test for the nonlinear method. Both approaches consistently detected structured networks of physiological interactions, revealing (i) strong internal information in all systems; (ii) information transfer directed predominantly from heart to brain; (iii) bidirectional interactions between HF and β EEG power. Moreover, the nonlinear method evidenced higher information flowing out of the δ node. These results highlight the potential of the information-theoretic framework to assess linear and nonlinear dynamics manifested in the functional network that underlies the autonomic regulation of cardiovascular and brain functions during sleep.

1. Introduction

The dynamics of complex physiological systems can often be explained as emerging from the activity of multiple system components, which exhibit autonomous dynamics but also interact with each other producing nontrivial collective behaviours [1]. A typical example is the brain, in which several connected neural units can be interpreted as the nodes of a network that is functionally organized to serve specific physiologic or cognitive processes. Extending this view to the whole human organism, the brain can be seen as an individual physiological system that has the capability to store information but also to share information with other systems, like the cardiovascular system, in order to preserve the physiological function [2]. This complex exchange of information among physiological systems is state dependent: for instance, it is well known that sleep has a profound impact on both cardiovascular and brain regulation, and that the stage organization of sleep reflects rhythmic variations of the activity of the autonomic nervous system [3].

In this context, the present paper deals with the description of physiological networks framed in the field of information dynamics [4], which provides entropy-based measures quantifying how information is generated and then processed inside the observed network of interacting dynamic systems. Specifically, we aim at quantifying the structure of the networks of brain-cardiovascular and brain-brain interactions during sleep, considering the cardiovascular system and the brain as dynamical systems whose states are described by the overnight time course of the amplitude of the cardiac parasympathetic component of heart rate variability and of the different EEG waves, respectively. These networks are identified in 10 young healthy subjects by means of specific entropy-based measures of internal information and information transfer, i.e. the conditional self entropy (CSE) [5] and the transfer entropy (TE) [6]. In order to investigate the impact of nonlinear dynamics on the detected network structures, these measures are computed following both linear model-based (MB) and nonlinear model-free (MF) estimation approaches [7].

2. Information dynamics

Let us consider an overall dynamical system composed of M possibly interacting subsystems, and assume that the states visited by the subsystems across time are described by the stochastic process $\boldsymbol{S}=\{S_1,...,S_M\}$. The tools of information dynamic quantify the information kept internally in a target process $X\in\boldsymbol{S}$, and the information

transferred to X from a 'source' process $Y \in \boldsymbol{S}$, in the presence of the remaining M-2 processes collected in the vector $\boldsymbol{Z}=\boldsymbol{S}\setminus\{X,Y\}$. To explicitly account for the flow of time, let us further denote as X_n, Y_n and $\boldsymbol{Z}_n$ the random variables obtained sampling the processes at the present time n, and as $X_n^-=[X_{n-1}\ X_{n-2}\cdots]$, $Y_n^-=[Y_{n-1}\ Y_{n-2}\cdots]$ and $\boldsymbol{Z}_n^-=[\boldsymbol{Z}_{n-1}\ \boldsymbol{Z}_{n-2}\cdots]$ the vector variables describing the past of the processes. Internal information and information transfer are then defined as follows.

2.1. Internal information

The internal information of the scalar process X belonging to the multivariate process $\boldsymbol{S}$ is mathematically defined as the conditional mutual information between the present and the past of X, given the past of all other processes in $\boldsymbol{S}$:

$$S_{X|Y,\boldsymbol{Z}} = I(X_n; X_n^- \mid Y_n^-, \boldsymbol{Z}_n^-) . \quad (1)$$

This quantity, commonly denoted as conditional self entropy (CSE), is the amount of information contained in the past of the target process that can be used to predict its present above and beyond the information contained in the past of all other processes in the network [5]. The CSE is useful for the structural analysis of connected systems because it is related to the autonomous dynamics of an individual system embedded in a network, in the sense that a system without internal dynamics does not exhibit internal information [5].

2.2. Information transfer

The information transferred from the source Y to the target X is quantified by the well-known transfer entropy (TE), which is defined as the conditional mutual information between the present of X and the past of Y, given the past of X and of all other processes in $\boldsymbol{S}$:

$$T_{Y\to X|\boldsymbol{Z}} = I(X_n; Y_n^- \mid X_n^-, \boldsymbol{Z}_n^-) . \quad (2)$$

The TE quantifies the amount of information about the present of the target process that is explained from the past of the source above and beyond the information explained by the past of the target itself and of all other processes in the network. The definition provided in Eq. (2) refers to the 'multivariate' or 'partial' TE, which extends to the case of multiple systems the traditional TE originally defined for bivariate systems [6]. This measure is helpful to assess the structure of directional interactions between processes in the observed network, because it has been shown that a system without causal interactions does not exhibit information transfer [5].

2.3. Estimation methods

The practical computation of CSE and TE from time series data proceeds first expressing the definitions (1) and (2) by means of conditional entropy terms:

$$\begin{aligned} S_{X|Y,\boldsymbol{Z}} &= H(X_n;\mid Y_n^-, \boldsymbol{Z}_n^-) - H(X_n;\mid X_n^-, Y_n^-, \boldsymbol{Z}_n^-) \\ T_{Y\to X|\boldsymbol{Z}} &= H(X_n;\mid X_n^-, \boldsymbol{Z}_n^-) - H(X_n;\mid X_n^-, Y_n^-, \boldsymbol{Z}_n^-) \end{aligned} , \quad (3)$$

where $H(A|\boldsymbol{B})=H(A,\boldsymbol{B})-H(\boldsymbol{B})$ is the conditional entropy of the scalar variable A given the vector variable $\boldsymbol{B}$, and $H(\cdot)$ denotes entropy. Then, suitable (conditional) entropy estimators have to be employed to compute information dynamics from finite length realizations of the observed processes. In this study, we considered the two estimation approaches described briefly in the following and with more detail in Ref. [7].

The linear MB estimation of information dynamics computes each term in (3) using linear regression, and then exploits the relation existing between conditional entropy and prediction error variance:

$$H(A \mid \boldsymbol{B}) = 0.5 \log 2\pi e \sigma^2_{A|\boldsymbol{B}} , \quad (4)$$

where $\sigma^2_{A|\boldsymbol{B}}$ is the variance of the residuals of a linear regression of A on $\boldsymbol{B}$. In this study, the roles of A and $\boldsymbol{B}$ are taken respectively by the present of the target X_n and by any of the combinations between the past vectors X_n^-, Y_n^-, $\boldsymbol{Z}_n^-$ appearing in (3). Linear regression was performed through standard least squares estimation after approximating the past of the processes with p samples, where p was set according to the Bayesian Information Criterion [8].

The nonlinear MF approach is based on non-parametric entropy estimation, which can be very cumbersome because it is hampered by the bias that affects progressively the entropy estimates at increasing the dimension of the argument variables. To limit this bias, we adopted the nearest neighbour entropy estimator:

$$\hat{H}(\boldsymbol{B}) = -\psi(k) + \psi(N') + \frac{d}{N'} \sum_{n=1}^{N'} \log \varepsilon_n , \quad (5)$$

where ε_n is twice the distance from the n-th realization of $\boldsymbol{B}$ to its k-th neighbor (k=10 in this study) in the d-dimensional space spanning the N' available realizations of $\boldsymbol{B}$, and ψ is the digamma function. Such an estimator was combined with a non-uniform embedding procedure aimed at limiting as much as possible the dimension of the argument variables. The procedure aims at discarding the variables which are not relevant to the description of the target dynamics, ending up with an approximation of X_n^-, Y_n^-, and $\boldsymbol{Z}_n^-$ that includes only the lagged variables which contribute significantly to the description of X_n [9].

3. Protocol and data analysis

Ten healthy subjects (all males, 18-23 yrs) were monitored during the full night with a digital polygraph

acquiring EEG (Cz-Ax derivation, Ax mastoid reference, 100 Hz sampling rate) and ECG (lead II ECG, 200 Hz sampling rate). The time series representative of the brain activity were measured applying a Fast Fourier transform to all consecutive 5-s windows of the EEG, and computing the spectral power inside the δ, θ, α, σ, and β frequency bands; for each band, power values were averaged over non-overlapping windows of 60 s and then normalized to the full night mean power in the band. ECG analysis was carried out first upsampling the signal to 400 Hz, performing beat-to-beat detection of the R peaks, measuring the sequence of the consecutive RR intervals, and resampling uniformly the series to 8 Hz; then, power spectral analysis was performed for consecutive windows of 120 s overlapped by half, and the time series representative of the cardiac parasympathetic activity was obtained normalizing the power in the high frequency band (HF, 0.5-0.4 Hz) to the total power in the range 0.04-0.4 Hz. More details of these procedures are reported in [2,7].

For each subject, the six time series of the cardiac HF component and of the normalized EEG power were considered as realizations of the stochastic processes descriptive of the heart rhythm (process η) and of the five brain rhythms (processes δ, θ, α, σ, and β). Then, the CSE of each process and the TE between each pair of processes were estimated using the approaches described in Sect. 2.3. Before the analysis, each time series was normalized to zero mean and unit variance. The statistical significance of each computed CSE and TE measure was assessed exploiting the Fisher F-test for the linear MB estimator [2], and exploiting the statistical criterion based on randomization implicitly present in the non-uniform embedding procedure for the nonlinear MF estimator [9]. Moreover, for each CSE or TE detected as statistically significant, a test based on linear multivariate surrogate data was performed to assess the statistical significance of the contribution of nonlinear dynamics to the measure [7].

4. Results

Figs. 1 and 2 depict the results of MB and MF analyses collected in a network representation, in which arrows describe specific estimates of the CSE (gray scale) or the TE (brain-heart links: red scale; brain-brain links: blue scale); thickness and color intensity of each arrow are respectively proportional to the number of subjects for which the measure was detected as statistically significant (also reported close to the arrow) and to the magnitude of the measure.

Considering the MB analysis (Fig. 1), we found that brain-heart interactions occur mostly through a strong bidirectional interaction between the η cardiac wave and the β EEG wave. As to the other brain waves, we found a weaker information transfer, directed almost unidirectionally from heart to brain. The brain-brain

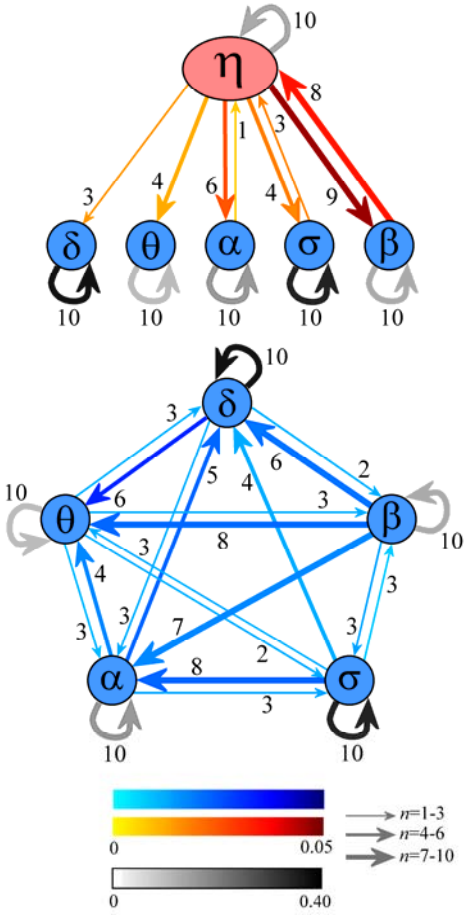

Figure 1. Networks of brain-cardiovascular (up) and brain-brain (down) interactions assessed through information dynamics computed using the MB estimator.

interactions formed a fully connected network, with information flowing mostly from the faster σ and especially β waves to the slower waves δ, θ and α. The internal dynamics assessed by the CSE were strong and significant for all rhythms.

The networks assessed through the nonlinear MF approach (Fig. 2) were overall similar to those obtained with the MB estimator, both in the magnitude and in the statistical significance of the estimates of CSE and TE. The MF analysis confirmed indeed the bidirectional interactions between the η and β nodes, the fully connected brain-brain network, and the existence of strong internal dynamics for all rhythms. The only notable exception regards the delta EEG rhythm, as also seen from Table 1 which collects the number of statistically significant incoming and outgoing TE links, together with the number of significant CSE values, assessed across subjects with the two approaches. For both estimators, we found more outgoing than incoming links for the η, β and σ network nodes, and more incoming than outgoing links for θ and α nodes. On the

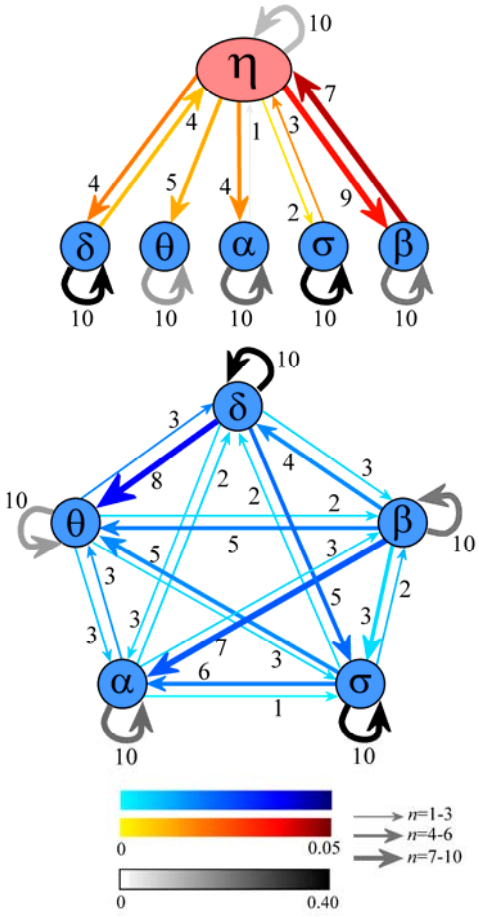

Figure 2. Networks of brain-cardiovascular (up) and brain-brain (down) interactions assessed through information dynamics computed using the MF estimator.

other hand, the δ node of the network was seen more as a sink for the information transfer using the MB estimator, and more as a source of information transfer using the MF estimator. Looking at the contribution of nonlinear dynamics to the information measures, the number of links for such a contribution was found to be statistically significant was remarkably higher for the CSE computed at the β node, and for the TE originating from the δ node.

Table 1. Number of significant network links assessed through MB and MF analysis of information dynamics.

	CSE		TE out		TE in	
node	MB	MF(NL)	MB	MF(NL)	MB	MF(NL)
η	10	10 (0)	26	24 (4)	12	15 (7)
δ	10	10 (1)	11	23 (14)	21	15 (7)
θ	10	10 (2)	11	11 (8)	25	26 (11)
α	10	10 (2)	13	10 (6)	27	23 (8)
σ	10	10 (1)	21	18 (6)	12	15 (8)
β	10	10 (5)	32	27 (11)	17	19 (11)

5. Conclusions

The present study showed how the combination of the emerging research fields of Network Physiology [1] and Information Dynamics [4] allows to explore the complex network of physiological interactions that sub-serves the joint regulation of cardiovascular and brain systems during sleep. Our findings reveal that both internal dynamics and causal interactions play a role in sustaining such a network, and both linear model-based and nonlinear-model free estimators are appropriate for structural analysis. While the model-based estimator is less demanding in terms of data length and computational load, we found that some fine structures – such as those underlying the internal dynamics of the β rhythm or the causal interactions involving the δ rhythm – could be better detected by the model-free approach which is sensitive to nonlinear dynamics.

Acknowledgements

This work was supported by the Healthcare Research Implementation Program (IRCS), Provincia Autonoma di Trento and Bruno Kessler Foundation, Italy.

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