Multivariate Linear and Nonlinear Central-Cardiorespiratory Coupling Pathways in Healthy Subjects

Steffen Schulz[1], Aniol Serra Juhé[2], Beatriz Giraldo[2], Jens Haueisen[3], Karl-Jürgen Bär[4], Andreas Voss[2]

[1]Ernst-Abbe-Hochschule, Institute of Innovative Health Technologies IGHT, Jena, Germany
[2]Universitat Politècnica de Catalunya, Department of Automatic Control (ESAII), Barcelona, Spain
[3]University of Technology, Institute of Biomedical Engineering and Informatics, Ilmenau, Germany
[4]University Hospital, Department of Psychiatry and Psychotherapy, Jena, Germany

Abstract

Advances in nonlinear dynamics and information theory facilitate a multivariate study of information transfer between physiological systems and sub-systems aiming to characterize healthy and diseased physiological network states. In this study, we investigated the central-cardiorespiratory network (CCRN) applying linear and nonlinear causal coupling approaches (normalized short time partial directed coherence, multivariate transfer entropy) in 21 healthy subjects. From all participants, continuous heart rate (successive beat-to-beat intervals, BBI), synchronized calibrated respiratory inductive plethysmography signal (respiratory frequency, RESP), and the mean power P_{EEG} from a 64-channel EEG were recorded for 15 minutes under resting conditions. We found that the central-cardiorespiratory coupling is a bidirectional one, with central driving mechanisms towards BBI (PEEG→BBI), and respiratory driving towards P_{EEG} (RESP→PEEG). The central-cardiac (P_{EEG}-BBI) and central-respiratory coupling (P_{EEG}-RESP) seem to be stronger generated by linear process than nonlinear ones. We obtained a different CCRN behavior in healthy subjects providing a further step towards a more comprehensive understanding of the interplay of neuronal and autonomic regulatory processes.

1. Introduction

The new interdisciplinary field of Network Physiology is getting more and more into the focus of interest in medicine. Network Physiology aims to develop theoretical framework and a system-wide network approach to understand how horizontal integration of physiological systems, each with its own complex structure and mechanisms of regulation, leads to global behaviour and distinct physiologic functions at the organism level [1]. It aims to define healthy and diseased states by analysing structural, dynamical and regulatory alterations in the interaction of physiological systems and sub-systems [2].

The central control of autonomic nervous system (ANS) and the complex interplay of its components can be described by a functional integrated mode - the central-autonomic-network (CAN) - and can be assumed as a feedback-feedforward network, reacting with flexible and adaptive responses to internal and external factors. CAN represents the integrated function and interaction between, the central nervous system (CNS) and ANS (especially the parasympathetic and sympathetic activity). The dynamic interplay between the brain and the heart ensure fundamental homeostasis and mediate a number of physiological functions as well as disease-related alterations [3]. It has been assumed that various autonomic function processes are generated by a network of interaction showing specificity for task and autonomic division. For healthy ones, Beissner et al. [4] suggested that asymmetric frontal EEG responses to emotional arousal in the form of positive and negative emotions may elicit different patterns of cardiovascular reactivity.

Recent advances in nonlinear dynamics and information theory facilitate a multivariate study of information transfer between time series. For the analyses of the cardiovascular-, cardiorespiratory- and central regulatory networks as well as the quantification of their interactions, a variety of methods have been proposed. For the characterization of linear and nonlinear couplings in the brain-heart (CNS-ANS) network several concepts are available [1, 5-7] based on Granger causality; nonlinear prediction; entropies; symbolization and phase synchronization [2].

The multivariate coupling analysis of heart rate (HR), respiration (RESP) and the power derived from the electroencephalogram (P_{EEG}) time series, respectively, might provide additional information about the complex central-autonomic-network in neuropathological diseases than uni- and bivariate approaches can do.

The aim of this study was to investigate the central-cardiorespiratory network (CCRN) by determining the strength and direction of the interaction between central- and autonomic network activity in healthy subjects under resting conditions.

2. Materials and Methods

2.1. Subjects

In this study, 21 healthy subjects (CON; 6 females, mean age 36.7±13.4 years) were enrolled. Interviews and clinical investigations were performed for CON to exclude any potential psychiatric or other diseases, as well as to double-check for any interfering medication. The structured clinical interview and a personality inventory (Freiburger Persönlichkeitsinventar) were also applied to the subjects to detect personality traits and any disorders which might influence autonomic function. All participants provided their written informed consent to a protocol approved by the local ethics committee of the Jena University Hospital. This study complies with the Declaration of Helsinki.

2.2. Data Recordings and Pre-processing

From all subjects, a 3-channel short-term ECG (500Hz), synchronized calibrated respiratory inductive plethysmography signal (50Hz) (LifeShirt®, Vivometrics, Inc., Ventura, CA, USA) and a 64-channel EEG (500Hz) were recorded synchronously for 15 minutes. The EEG (Brain Products, Germany) was acquired using 64 active Ag/AgCl electrodes, and transmitted via the BrainAmp Amplifier (AFZ: ground, FCZ: reference). The electrodes were positioned according to the extended 10-20-system using an electrode cap. The impedance levels (<25 KΩ) for all electrodes were checked following the attachment of the electrode cap to each participant's scalp. All subjects' recordings were started after a supine resting period of 10 minutes. Subjects were asked to close their eyes, relax and breathe normally to avoid hyperventilation.

The following time series with respect to autonomous regulation were automatically extracted from the raw data records:

- Heart rate (lead I) consisting of successive beat-to-beat intervals (BBI, [ms]),
- Respiratory frequency (RESP, [s]) as the time intervals between consecutive breathing cycles,
- Mean power P_{EEG} from the EEG (during each RR-interval, [μV^2]).

EEG recordings (without any stimulation) were band-pass filtered (0.05Hz-60Hz, Butterworth filter, order=3) in order to remove slow drifts resulting from slow body movements or sweating, and to prevent higher frequency content from additional noise. For EEG analyses, artefact-free time series were used. All extracted time series (autonomous, central) were filtered by applying an adaptive variance estimation algorithm to remove and interpolate seldom occurring ventricular premature beats and artefacts (e.g., movement, electrode noise, and extraordinary peaks) to obtain normal-to-normal beat time series (NN). To obtain synchronized time series, BBI, RESP, and P_{EEG} were resampled using a linear interpolation method (2Hz).

2.3. Normalized Short-time Partial Directed Coherence

To quantify the central-cardiorespiratory network the NSTPDC approach was applied [8]. It is based on a multivariate autoregressive model with model order p to determine linear Granger causality (GC) in the frequency domain based on the time-variant partial directed coherence approach (tvPDC). For the selection of the optimal order p of the AR(p) model the stepwise least squares algorithm and the Schwarz's Bayesian Criterion (SBC) were used.

The normalization factor NF determines the strength and the direction of all causal links between a set of multivariate time series as a function of frequency f. The NF can take the following values: NF = {−2, −1, 0, 1, 2}. Strong unidirectional coupling is indicated if NF is equal −2 or 2, bidirectional coupling with the determination of the driver-responder relationship exists if NF is equal−1 or 1, and an equal influence in both directions and/or no coupling if NF=0. In the case that both area indices reveal equal values that are larger than zero an equal influence in both directions is present, if both area indices reveal equal values but are zero no coupling is present. Here, NSTPDC indices were calculated by applying a window (the Hamming window) of lengths l, with l=120 samples and a shift of 30 samples (90 samples overlap between each window).

In addition to NF, the areas ($A_{BBI\rightarrow PEEG}$, $A_{PEEG\rightarrow BBI}$, [a.u.]) were determined to identify the coupling strength. $A_{BBI\rightarrow PEEG}$ and $A_{PEEG\rightarrow BBI}$ can have any values in the range of [0,1]. $A_{PEEG\rightarrow BBI}$=1 indicates that all causal influences originating from central part are directed toward BBI, $A_{PEEG\rightarrow BBI}$=0 indicates that the central part does not influence BBI.

2.4. Multivariate Transfer Entropy

Schreiber [9] proposed an information theoretic approach called transfer entropy (TE) to distinguish between driving and responding elements, to detect asymmetries in the interaction, and to quantify the extent to which the dynamics of one process influences the conditioned transition probabilities of another. TE

measures GC with the prediction improvement approach and extends the concept of Shannon entropy by taking into account the probabilities of transitions rather than static probabilities. TE is able to determine the direction of coupling and information flow between coupled processes, and it is "model-free" approach [7]. Vakorin et al. [10] introduced the partial transfer entropy, a multivariate version of TE which quantifies causality between two nodes of an interacting network.

The Multivariate Transfer Entropy (MuTE) quantifies causality from one time series to another as the amount of information flowing directly from the first to the second time series, while accounting for the effects of all other time series in the multivariate representation. Here, MuTE was applied using the nearest neighbour estimator and non-uniform embedding (NN NUE) to quantify the nonlinear interactions [11].

3. Results

We found that the central-cardiorespiratory coupling is a bidirectional one, with central driving mechanisms (P_{EEG}→BBI) towards BBI, and respiratory driving (RESP→P_{EEG}) towards P_{EEG}.

The linear influence (NSTPDC method) from P_{EEG} to BBI was much stronger than BBI to P_{EEG}, whereas the linear influence from RESP to P_{EEG} was much stronger than P_{EEG} to RESP (figure 1, table 1).

The nonlinear influences (MuTE method) from BBI and RESP to P_{EEG} as well as from P_{EEG} to BBI and RESP were nearly equally strong pronounced (table 1).

For the coupling between BBI and P_{EEG} it was shown that mean NF was −0.67 pointing to a bidirectional coupling from P_{EEG}→BBI, with the driver being P_{EEG}, and BBI the target variable. For the coupling between the respiration (RESP) and P_{EEG} we revealed a mean NF of 0.82, indicating bidirectional coupling from RESP→P_{EEG}.

Table 1. Results of CCRN analysis applying NSTPDC and MuTE for healthy subjects (CON).

	coupling strength	CON mean ± sd
MuTE	BBI→P_{EEG}	0.016 ± 0.011
	P_{EEG}→BBI	0.017 ± 0.011
	RESP→P_{EEG}	0.017 ± 0.010
	P_{EEG}→RESP	0.016 ± 0.009
NSTPDC	BBI→P_{EEG}	0.10 ± 0.05
	P_{EEG}→BBI	0.19 ± 0.10
	RESP→P_{EEG}	0.17 ± 0.07
	P_{EEG}→RESP	0.07 ± 0.06

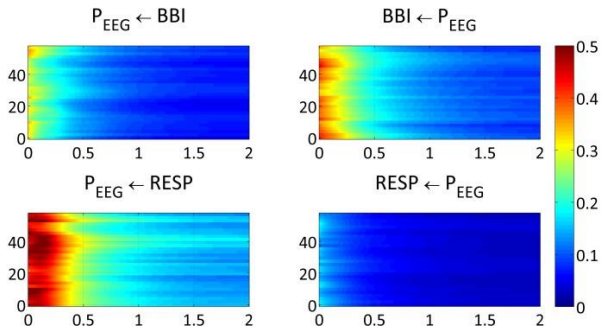

Figure 1. Averaged NSTPDC plots for central-cardiorespiratory coupling analyses for healthy subjects. Arrows indicating the causal coupling direction from one time series to another, e.g., RESP←P_{EEG}, indicating the causal link from P_{EEG} to RESP. Coupling strength ranges from blue (no coupling) to red (maximum coupling), where RESP represents respiratory frequency, and P_{EEG} represents the mean power in BBI-related EEG intervals.

4. Discussion

We found a different CCRN structure in healthy subjects expressed by a strong central influence on the cardiac system, and a strong respiratory influence on the central nervous system, respectively. The central-cardiac (P_{EEG}-BBI) and central-respiratory coupling (P_{EEG}-RESP) seem to be more clearly indicated by the linear method than the nonlinear one. Particularly the central nerve system stronger controls the cardiac and less the respiratory system. This suggests that the central-cardiorespiratory process (closed-loop) is mainly focusing on adapting the heart rate rather via the autonomic nerve system than via the central influence on the respiratory system. On the other side, the feedback-loop from ANS to CNS is strongly dominated by the respiratory activity. This behavior may be interpreted as a stronger information flow from RESP to central regulatory processes acting as a feedback-loop to central activity for more inputs (information flow) toward ANS. The final respiratory output involves a complex interaction between the brainstem and higher centers, including the limbic system and cortical structures. Respiration is primarily regulated for metabolic and homeostatic purposes in the brainstem and changes in response to emotions, such as sadness, happiness, anxiety or fear [12]. Since the human organism is an integrated network of interconnected and interacting organ systems, each system represents a separate regulatory network. The behavior of one single physiological system (network) may affect the dynamics of all other systems in the entire physiologic network. Due to these interactions, failure of one system can trigger a cascade of failures throughout the entire network [13]. Bartsch et al. [14] could demonstrated that the cardiac and respiratory systems exhibit three distinct independent forms of cardio-respiratory coupling

(RSA, cardio-respiratory phase synchronization (CRPS) and time-delay stability (TDS)) responding differently to key physiologic parameters, and act on different time scales on neuro-autonomic control. The output of the CAN is directly linked to heart rate variability (HRV). In addition, sensory information from different organs and subsystems such as the heart, the immune system and vascular system are feedbacks to the CAN. As such, HRV is an indicator of central-peripheral neural feedback and CNS-ANS integration [15].

In conclusion, this study provides a further step towards a more comprehensive understanding of the interplay of neuronal and autonomic regulatory processes in healthy subjects. This might be the basis for an early identification of central and/or autonomic impairments.

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Address for correspondence.

Prof. Dr. Andreas Voss
Ernst-Abbe-Hochschule Jena
Institute of Innovative Health Technologies IGHT
Carl-Zeiss-Promenade 2, 07745 Jena, Germany
Phone: 49-3641-205-625
E-Mail: andreas.voss@eah-jena.de