Causal Linear and Non-linear Assessment of Central-Cardiorespiratory Network Pathways in Healthy Subjects in Comparison to a Neurological Disorder (Schizophrenia) under Resting Conditions

A. Voss
Ernst-Abbe-Hochschule Jena
Institute of Innovative Health Technologies, Jena, Germany

The aim of network physiology is to gain a better understanding of how the various integrated physiological systems and subsystems with their complex structures and regulatory mechanisms describe the global behavior and different physiological functions of the entire organism.
In particular, the focus has moved towards the multivariate assessment of the strength and the direction of such couplings for a better understanding of physiological regulatory mechanisms.

Physiological background
The complex interplay of the cardiovascular and cardiorespiratory system and their subsystems (fig. 1) can be described as linear and nonlinear closed loops with their feedforward and feedback mechanisms.

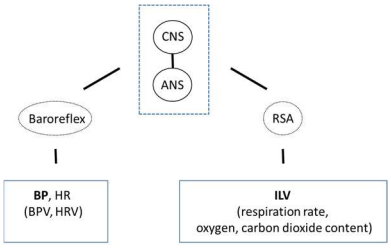

Fig. 1: Extremely simplified overview of the central/autonomous regulation of blood pressure and respiration (CNS - central nervous system, ANS – autonomic nervous system, RSA – respiratory sinus arrhythmia, BP – blood pressure, HR – heart rate, BPV –blood pressure variability, HRV – heart rate variability, ILV – instantaneous lung volume)

The respiratory system combines the biomechanics of breathing, ventilation and gas exchange. Heart pumping and blood flow are strongly influenced by various factors and events, such as oxygen demand, physical activity, stress, temperature and respiration. Respiratory phase-driven fluctuations in venous filling, stroke volume, cardiac output and peripheral blood flow contribute to fluctuations in heart rate and blood pressure. While changes in the cardiovascular system can lead to changes in respiration, the influence of respiration on the cardiovascular system appears to be stronger. This is the reason why in this study we have dealt in particular with cardio-respiratory coupling.

The high frequency (HF) oscillations within the heart rate variability (HRV) coincide with the typical respiration frequency and, hence, are related to the phasic effects of tidal respiration on the cardiovascular system (mechanical, hemodynamic and cardiorespiratory mechanisms), whereas the low frequency (LF) oscillations are thought to correspond to cardiac feedback mechanisms that are slower than and independent of respiration. The baroreflex monitors arterial blood pressure and responds to acute changes via central–neural–autonomic pathways (in the medulla oblongata). The respiratory sinus arrhythmia (RSA) is HRV in synchronization with the phases of respiration, wherein the R-R intervals during inspiration are shortened and during expiration extended. The maximization of RSA/HRV at approximately 6 breaths per minute indicates a resonance of the cardiorespiratory system and is therefore referred to as the "resonance frequency effect". The proposal of a “respiratory gate” was an attempt to characterize the autonomic modulation of the heartbeat by the cardiorespiratory centers (within the nucleus tractus solitarius - NTS). RSA is thought to have a distinct physiological significance, though it has not been fully elucidated.

Both arms of the autonomous nervous system (sympathicus, parasympathicus) are under control of the central respiratory centers, where the autonomous drive of the reflex mechanisms and the lung extension receptors converge. Autonomic outflow is inhibited during inspiration and disinhibited during expiration. The influence of the respiratory phase on cardiovagal activity is considered far more significant due to a more direct central neuronal drive mechanism and the speed of parasympathetic signal transduction and action that allows heart rate modulation at all respiratory frequencies.

Several brain areas are responsible for regulating the sympathetic and parasympathetic outflow:

- Cortex
- Subcortical forebrain
- Midbrain
- Medulla

and thus, the autonomous cardiovascular and cardiorespiratory regulations.

Different studies using both pharmacological and neuroimaging approaches have provided evidence that the activity of the prefrontal cortex is associated with vagally mediated HRV. Psychopathological states such as schizophrenia (SZO) are associated with prefrontal hypoactivity and a lack of inhibitory neural processes reflected by a poor habituation to novel neutral stimuli, a pre-attentive bias for threat information, deficits in working memory and executive function, and poor effective information processing and regulation. Psychopathological states such as in schizophrenia as a neurologic disease are associated with prefrontal hypoactivity and a lack of inhibitory neural processes reflected by a poor habituation to novel neutral stimuli, a pre-attentive bias for threat information, deficits in working memory and executive function, and poor effective information processing and regulation

For the quantitative analysis of the brain-heart (CNS-ANS) network coupling pathways and its integrated interacting subsystems as the cardiovascular- and cardiorespiratory system several univariate and multivariate linear and nonlinear approaches from nonlinear dynamics and information theory domains have been developed.

This study aims to characterize short-term instantaneous central-autonomic-network coupling pathways (top-to-bottom and bottom to top) by analyzing the interactions of heart rate, respiration and central activity (from EEG) in schizophrenic patients and healthy controls. It is based on previous studies in which only the cardiorespiratory (no central component) coupling in other patient groups was investigated.

Methods

We enrolled 17 patients with paranoid SZO (two females, 37.5 +/-10.4 years) and 17 age-gender healthy subjects (CON; four females, 37.7 +/-13.1 years).
For all patients and controls, a 3-channel ECG (500 Hz), a non-invasive continuous blood pressure (200 Hz, Portapres Model-2), calibrated respiratory inductive plethysmography signal (LifeShirt), and a 64-channel EEG (extended 10-20-system, Brain Products, 500 Hz) were recorded synchronously for 15 minutes.
The following time series with respect to the autonomous regulation were automatically extracted from the raw data records:

- HR (lead I) consisting of successive beat-to-beat intervals (BBI, (ms)), and
- RESP (s) as time intervals between consecutive breathing cycles.

In relation to the extracted BBI (figure 2), the corresponding time intervals (from the EEG raw data recordings) were extracted as EEG(i) (ms). Within each BBI(i), with i (i = 1:R-1) as the successive number of R-peaks (R), the mean power PEEG(i) (μV2) of EEG(i) was calculated to obtain the new time series representing the central component. The frontal lobe with the related EEG electrodes were analyzed in this study.

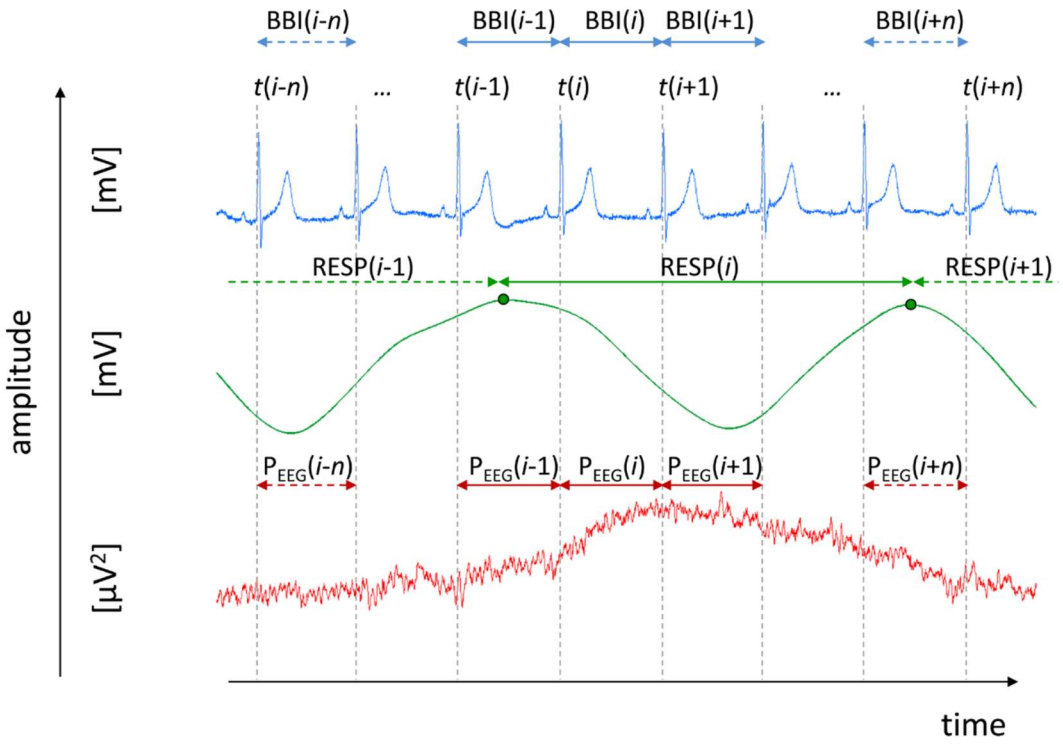

Figure 2. Example of the analyzed raw data recordings and the extracted time series. Raw data are from top to bottom: ECG, synchronized calibrated respiratory inductive plethysmography signal (RESP) and EEG. BBI(i) represents the beat-to-beat intervals, RESP(i) represents the respiratory frequency as time intervals between consecutive breathing cycles, and PEEG(i) specifies the mean power in the time intervals of the EEG raw data (electrode: Fp1) in relation to BBI(i).

RSA was quantified in the time domain using the peak-to-valley approach.

For the characterization of linear and nonlinear couplings, we applied the normalized short-time partial directed coherence (NSTPDC) and the Multivariate Transfer Entropy (MuTE).
NSTPDC based on an m-dimensional multivariate autoregressive model (MAR) process with model order p to determine Granger causality in the frequency domain. It is based further on the time-variant partial directed coherence approach providing information about the partial correlative short-time interaction properties of non-stationary signals, with f as the frequency and n as the number of windows (a detailed description you can find elsewhere).

$$CF = \frac{\frac{1}{n}\sum \pi_{xy}(f,n)}{\frac{1}{n}\sum \pi_{yx}(f,n)}$$

The introduced normalized coupling factor determinates the direction of the causal connections between the investigated time series as a function of frequency f. For determining the coupling strength between two time series, the areas generated in space by the coupling factor CF were estimated in each window within the frequency band f = 0–2 Hz and afterwards averaged.

The Multivariate Transfer Entropy is based on Transfer Entropy (TE) to detect the information transfer between joint processes:

$MuTE_{X \to Y/Z}$

The Multivariate Transfer Entropy (MuTE) extends the classical TE to the case of multiple interacting processes and discovers purely nonlinear interactions with a range of interaction delays.

Results

Comparing the general univariate indices led to the results (schizophrenics in relation to healthy controls) presented in table 1.

Table 1: Univariate indices (with meanNN as mean value, sdNN as standard deviation of successive RR-intervals, RESPV as respiration variability, BF as breathing frequency, and P as Power of the EEG signal.)

HRV	meanNN	↓↓
	sdNN	↓↓
RESPV	meanNN_RESP	↓
	BF	↑
	*t*inspiration	↓
	*t*expiration	↓
RSA	RSA	↓↓
EEG	*P*	↓↓

Linear and nonlinear cardiorespiratory coupling analyses revealed the results (discriminating SZO and CON) showing in table 2.

*Table 2: Results of central-cardiorespiratory coupling analyses (→ means a causal link from x to y; * p<0.01, ** fulfilling the Bonferroni-Holm criterion)*

Coupling direction			Coupling strength	
		p	**CON**	**SZO**
			mean ± sd	**mean ± sd**
MuTE	BBI→P_{EEG}	*	0,014 ± 0,011	0,012 ± 0,011
	P_{EEG}→BBI	n.s.	0,016 ± 0,010	0,014 ± 0,010
	RESP→P_{EEG}	**	0,017 ± 0,010	0,014 ± 0,009
	P_{EEG}→RESP	**	0,015 ± 0,008	0,012 ± 0,009
	BBI→RESP	**	0,020 ± 0,013	0,015 ± 0.012
	RESP→BBI	**	0,033 ± 0,009	0,026 ± 0.012
NSTPDC	BBI→P_{EEG}	**	0,10 ± 0,05	0,12 ± 0,05
	P_{EEG}→BBI	*	0,19 ± 0,10	0,16 ± 0,10
	RESP→P_{EEG}	**	0,17 ± 0,07	0,23 ± 0,10
	P_{EEG}→RESP	**	0,07 ± 0,06	0,06 ± 0,05
	BBI→RESP	**	0,05 ± 0,02	0,04 ± 0.03
	RESP→BBI	n.s.	0,25 ± 0,08	0,27 ± 0,17

Discussion

We could demonstrate a considerably significantly different central-cardiorespiratory and cardio-respiratory network behaviour in schizophrenia in comparison to CON.
In contrast to the non-linear approach the linear one revealed increased central-cardiorespiratory couplings in the direction towards the central component ((BBI→P_{EEG}, RESP→P_{EEG}). MuTe and NSTPDC showed further a significant decrease in the central-respiratory information flow (P_{EEG}→RESP) and

almost no influence on the central-cardiac ((P_{EEG}→BBI)) information flow. Finally, the coupling between RESP and BBI was reduced in SZO, only MUTE could reveal a nearly unchanged RESP→BBI coupling.

The respiratory network receives peripheral chemosensory and mechanosensory inputs and modulatory inputs from the other parts of the brain. These inputs are essential for adaptive changes in the respiratory motor output, ensuring appropriate ventilation of the lungs in variable environmental and physiological conditions. This might be one reason for the increased coupling RESP→P_{EEG} where the ANS dominates. It seems to be that in SZO maintaining the oxygen supply takes priority expressed by this stronger feedback from RESP towards P_{EEG}. Several articles have reported that heart rate variability is significantly reduced in schizophrenic patients. Here one could speculate that the increased linear information flow BBI→P_{EEG} is associated with the attempt of the ANS to achieve counterregulation by the CNS.

One limitation of this study is that the enrolled SZO patients were treated with atypical neuroleptics and therefore a side effect of these drugs cannot be completely excluded on HRV and coupling results.

In summary, we could demonstrate a considerably significantly different central-cardiorespiratory network behaviour in schizophrenia with decrease information flows from central to the autonomic regulation and an increased strong influence especially of the respiratory system on the central nervous system.
Moreover, this study provides a more in-depth understanding of the interplay of the central and autonomic regulatory network in healthy subjects and schizophrenia.

Outlook

It would be very promising to combine fMRI and EEG analysis to get new perspectives in cognitive functions in respect to the central-autonomic-network in SZO.
In this study we evaluated the general behaviour of the underlying short-term couplings and an averaging of features (windows) over time was performed (no real-time analyses). From the methodical aspect, it would be interesting in ongoing studies to prove if other coupling approaches (e.g. time-invariant approach based on Granger causality, recurrence quantification analysis, functional connectivity analysis approaches…) would reveal new and more detailed information. Further on, it would be worth to normalize the output of the MuTe approach.
It would also be of interest to investigate the influence of different pharmaceuticals.
Finally, a detailed examination of the central component by evaluation in the individual EEG frequency bands could provide further detailed information on the involved brain locations.

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