Analysis of interconnection between central nervous and cardiovascular systems

In the paper the aspects of collaboration and interconnection between central nervous and cardiovascular systems are described. Existing methods to estimate the connectivity between HRV and EEG signals and corresponding up-to-date studies are reviewed. It can be affirmed that there is an apparent interconnection between central nervous and cardiovascular systems on the basis of examined papers. But the definite method of assessment of this interconnection capable to take into account the underlying manner of this connection is yet to be defined. It was determined that further research should be directed into examination of non-linear connectivity between HRV and EEG signals, methods for non-linear connectivity assessment and comparison of their performance. On this basis the new ways to improve the current approaches are expounded. Reference 29, figures 1.

Keywords: EEG, HRV, interconnection, correlation, transfer entropy.

Introduction

The study of interconnection between central nervous system (CNS) and cardiovascular system (CVS) is of great importance for understanding their physiology, control and regulation. Biomedical signal analysis of these systems of human body provides valuable information to estimate functioning of the autonomous nervous system (ANS). Up to date research include following areas of problems:

- detecting and assessment of physiological state changes e.g. altered states of consciousness as in sleep and meditation;
- use of heart rate variability in assessment of sleep quality and sleep stages;
- estimation of driver drowsiness;
- quantification of respiratory sinus arrhythmia (RSA);
- development of a reliable tool for diagnosis of various diseases, such as sleep disorders, epilepsy etc.

To index the central control of the heart via the vagus nerve heart rate variability data are widely used. Heart is dually innervated by the autonomic nervous system such that relative increases in sympathetic activity are associated with heart rate increases and relative increases in parasympathetic activity are associated with heart rate decreases [14].

Nowadays studying the functioning of brain is possible with electroencephalography, magnetoencephalography and functional imaging methods, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The role of brainstem in controlling of cardiac output through autonomic nervous system has been well established. However, there is still a lot of uncertainty on what kind of roles the different parts of cerebral cortex have on the regulation of cardiac system [13].

Despite availability of many research papers about studying CNS and CVS separately, using very sophisticated mathematical techniques, there is still a huge gap in understanding the CNS and CVS interconnections. The goal of the present work is to review existing approaches to the analysis of interaction between central nervous and cardiovascular system. Special effort will be made to clarify the techniques that are used to estimate connections between cerebral cortex and cardiovascular system. On this basis the correct directions of investigations will be defined to undertake the further investigation of the interaction that involves analysis of EEG and HRV signals.

1. Collaboration and interconnection of two systems

In 1865 Claude Bernard delivered a lecture at the Sorbonne on the physiology of the heart and its connections with the brain. His work denoted the first step to systematically investigate the connections between heart and brain [28]. Since then ceaseless efforts had been made to push further our understanding of connections between two cardinal systems of human body.

The easiest and most intuitive approach of assessment of interconnection between central nervous system and cardiovascular system is the analysis of signals of electrical activity of cerebral cortex and heart.

The ECG is the most commonly used technique to detect and diagnose heart diseases and to
monitor therapies that influence heart electrical activity. It is noninvasive, virtually risk free, and relatively inexpensive. Since its introduction, a large database has been assembled correlating the ECG waveform recorded from the body surface to the underlying electrical activity of individual cardiac cells on the one hand, and to the clinical presentation of the patient on the other, thereby providing insight into the electrical behavior of the heart and its modification by physiologic, pharmacologic, and pathologic events [22]. To sum up, ECG and derived heart rate fluctuations can be easily recorded and analyzed providing not only the information about electrical activity of heart but also the inner regulation of CVS by CNS that will be described in detail below.

Heart rate fluctuations, or heart rate variability, is defined as change of heart period during consecutive beats. These changes are due to various parameters: sympathetic innervation through thoracic efferents on the SA node, parasympathetic innervation through the vagus nerve on the SA node, circadian rhythms, fluctuations related to plasma renin activity, thermoregulatory cycles and, maybe, other yet unknown parameters [6]. Measures of heart rate variability are increasingly being employed in applications ranging from basic investigations of central regulation of autonomic state to studies of fundamental links between psychological processes and physiological functions, evaluations of cognitive development and clinical risk. As psychological correlates and physiological mechanisms are being delineated, measures of heart rate variability may offer powerful tools for the clarification of relationships between psychological and physiological processes [22]. In the present paper heart rate variability will be regarded as a signal that could provide insight into the heart regulation by the CNS.

Electroencephalogram (EEG) is a recording of electrical activity on scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain [18]. In neurology, the main diagnostic application of EEG is in the case of epilepsy, as epileptic activity can create clear abnormalities visible during a standard EEG study [3]. EEG is also used for the diagnosis of encephalopathies, sleep and sleep disorders, brain death, focal brain disorders and coma.

Like many organs in the body, the heart is dually innervated. Although a wide range of physiologic factors determine cardiac functions such as heart rate (HR), the autonomic nervous system is the most prominent. Importantly, when both cardiac vagal (the primary parasympathetic nerve) and sympathetic inputs are blocked pharmacologically (for example, with atropine plus propranolol, the so-called double blockade), intrinsic HR is higher than the normal resting HR. This fact supports the idea that the heart is under tonic inhibitory control by parasympathetic influences. Thus, resting cardiac autonomic balance favors energy conservation by way of parasympathetic dominance over sympathetic influences. In addition, the HR time series are characterized by beat-to-beat variability over a wide range, which also implicates vagal dominance as the sympathetic influence on the heart is too slow to produce beat to beat changes. There is an increasing interest in the study of heart rate variability among researchers from diverse fields. Low heart rate variability (HRV) is associated with increased risk of all-cause mortality, and low HRV has been proposed as a marker for disease [27].

Modulation of autonomic function by the cerebral cortex has been recognized for many decades, although the place of the cerebral cortex in the hierarchy of central autonomic regulatory circuits has only been identified relatively recently. Research has identified the major pathways and connections of the medial prefrontal cortex and insular cortices, but the relative importance of these pathways in mediating changes in autonomic function is still emerging [15].

Although novel observations about cortical influences on autonomic processing are coming from modern imaging techniques, their relatively low spatial resolution limits the ability of researchers to identify the cortical neurons that influence central autonomic control in humans. The cerebral cortex is now known to influence gastrointestinal function, regional hemodynamics, and sympathetic vasomotor outflow. The neural pathways that mediate cortically evoked changes in autonomic function are better understood than 20 years ago, but much remains to be learned [15].

In studies that relate cerebral blood flow to HRV it is shown that several areas including the amygdala and the medial prefrontal cortex (mPFC) that are involved in perceptions of threat and safety are also associated with HRV. The meta-analysis in paper [27] provides support for the idea that HRV may index the degree to which a mPFC-guided core integration system is integrated with the brainstem nuclei that directly regulate the heart. Thus these results support Claude Bernard's idea that the vagus serves as a structural and functional link between the brain and the heart. HRV may index important organism functions associated with adaptability and health [27].
2. Signal analysis techniques for separate investigation of two interconnected systems

2.1. HRV components. Linear analysis

Periodic components of heart rate variability tend to aggregate within several frequency bands. In young healthy individuals at rest, the most conspicuous of these bands is at the respiratory frequency [7]. During controlled rest condition, the regular breathing produces a well-defined spectral component around the respiratory frequency. However, in real conditions, respiration can be extremely variable and irregular, affecting the HRV spectrum in a wider range of frequency such as in presence of stationary wide-band respiratory activity [16].

The respiratory frequency band is considered to range (nominally) from about 0.15 Hz to 0.4 Hz in humans but may extend below 0.15 Hz and up to 1 Hz or more for infants and for adults during exercise. Respiratory frequency is generally believed to be mediated predominantly by fluctuations of vagal-cardiac nerve traffic and thus may provide an index of vagal activity. R-R interval oscillations also occur at low frequencies (about 0.05-0.15 Hz), including a 0.1-Hz component that is sometimes referred to as the 10-s rhythm or the Mayer wave. This frequency range has been termed the m/d-frequency band by some authors, but the designation of low frequency (LF) is more common. The LF heart rate rhythms have been suggested to reflect mainly sympathetic outflow but are thought by most investigators to be of both sympathetic and vagal origin [7]. Sometimes the respiratory peak may also overlap LF component. In these cases, the correct quantification of respiratory sinus arrhythmia (RSA) is difficult and the separation between respiratory-related and unrelated RR variability may be crucial [16].

Other R-R interval fluctuations occur at frequencies below 0.05 Hz. These have been designated variously, but commonly used bands include very low frequencies (VLFs; about 0.003-0.05 Hz) and slower, ultra low frequencies (ULFs) that include circadian rhythms. The VLF R-R interval oscillations have been studied much less than higher frequency rhythms and may reflect thermoregulatory cycles or fluctuations related to plasma renin activity. Circadian heart rate variability reflects a wide range of determinants, including changes of activity, posture, breathing, autonomic outflow, state of arousal, and a range of behavioral variables. Although VLF or slower rhythms of heart rate may have important clinical applications and psychophysiological correlates, their origins and mechanisms remain unclear [6].

Heart rate variability is traditionally quantified by linear methods for time and frequency (spectral) domain analysis providing information about heart rate variability magnitude and frequencies. Short-term heart rate variability spectral analysis allows to isolate faster high frequency respiratory-coupled influences on the heart rate variability (HF-HRV: 0.15-0.4 Hz) from slower sources of the heart rate variability (LF-HRV: 0.04-0.15 Hz). It seems that the oscillations in cardiac sympathetic nerve activity make a minor contribution to the heart rate oscillations at low-frequency component (LF-HRV); and these oscillations are derived mainly from a baroreflex, vagally mediated response to blood pressure Mayer waves. In contrast, high-frequency cardiac rhythms are mediated primarily by vagal innervation of the sinoatrial node reflecting the RSA. The RSA mechanisms include central medullary generator, reflexes from the lungs, baroreflexes, chemoreflexes, as well as local mechanisms (stretching of the sinoatrial node etc.). RSA is mediated predominantly by fluctuations of vagal cardiac nerve efferent traffic originating in the nucleus ambiguous and therefore provides a noninvasive index of cardiac vagal regulation. The nucleus ambiguous is considered as an origin of the more recently developed smart vagus to facilitate the complex emotion responses and social behavior. Two sources of structural evidence link RSA to emotion. Efferent fibers from the nucleus ambiguous innervate the larynx, an important structure for communication of emotional state through vocalization. Also, the nucleus ambiguous fibers are believed to terminate in the source nuclei of the facial and trigeminal nerves, which facilitate the emotion behaviors of facial expression and vocalization. Recently, along with structural evidence, empirical studies relating RSA to emotion in humans have accumulated. Therefore, the RSA should be considered as an index of both cardiac vagal and emotional regulation [28].

2.2. HRV nonlinear analysis

The physiological cardiac control mechanisms integrated from subcellular to systemic levels operate over multiple time scales. This perpetual control results in the complex oscillations of the heart rate the measured output signal is characterized by great complexity. Recently, nonlinear methods measuring qualitative characteristic of the cardiac time series i.e. complexity, and other system dynamic features have been shown to be more suit-
2.3. EEG analysis

EEG analysis within the analyzed signal is a complex task due to the multi-scaled nature of the signals. The complexity for various time scales of fluctuations cannot be measured by traditional entropy measures, including SampEn, fail to account for the complexity of heart rate fluctuations. Firstly, the complexity analysis of heart rate variability was performed by calculation of Approximate Entropy (ApEn) [20]. An improved version of ApEn is a measure of Sample Entropy (SampEn) [21] which quantifies the irregularity and unpredictability of a time series. Since heart rate time series under healthy conditions have a complex spatial and temporal structure with correlations on multiple scales, single-scale based traditional entropy measures, including SampEn, fail to account for the multiple time scales inherent in the physiologic systems dynamics. A meaningful measure of the complexity should take into account multiple time scales. Multiscale entropy analysis describes the complexity for various time scales of fluctuations within the analyzed signal.

2.3. EEG analysis

Many brain disorders are diagnosed by visual inspection of EEG signals. The clinical experts in the field are familiar with manifestation of brain rhythms in the EEG signals. In healthy adults, the amplitudes and frequencies of such signals change from one state of a human to another, such as wakefulness and sleep. The characteristics of the waves also change with age. There are five major brain waves distinguished by their different frequency ranges.

There have been many algorithms developed so far for processing EEG signals. The operations include, but are not limited to, time-domain analysis, frequency-domain analysis, spatial-domain analysis, and multiway processing. Also, several algorithms have been developed to visualize the brain activity from images reconstructed from only the EEGs. Separation of the desired sources from the multisensor EEGs has been another research area. This can later lead to the detection of brain abnormalities such as epilepsy and the sources related to various physical and mental activities [23].

If the signals are statistically stationary it is straightforward to characterize them in either the time or frequency domains. The frequency-domain representation of a finite-length signal can be found by using linear transforms such as the (discrete) Fourier transform (DFT), (discrete) cosine transform (DCT), or other semi-optimal transform, which have kernels independent of the signal. The wavelet transform (WT) is another alternative for a time–frequency analysis. Unlike the short-time Fourier transform, the time–frequency kernel for the WT-based method can better localize the signal components in time–frequency space. As an effective tool for prediction and characterization of signals, deterministic chaos plays an important role. Although the EEG signals are considered chaotic, there are rules that do not in themselves involve any element of change and can be used in their characterization [23].

3. Connectivity estimators

When are two or more dynamical systems coupled? Although this issue has been extensively studied for linear systems, the interest in nonlinear dynamics and nonlinear (generalized) synchronization has renewed in this issue in recent years. Detecting coupling when the underlying equations are unknown, and when an arbitrary amount of measurement or dynamical noise is present is especially unclear [17]. Techniques capable to analyze the presence of connectivity, its strength and direction of influence between CNS and CVS should be used to get more information about state of human body.

3.1. Correlation

Correlation is a measure of strength of linear dependence between variables. The most common of various measures is Pearson correlation coefficient, that is used to estimate linear relationship between two variables. The conventional dictum that "correlation does not imply causation" means that correlation cannot be used to infer a causal relationship between the variables [5]. Nevertheless correlation can indicate the possibility of existence of causal relations.
In papers that study linear correlation between EEG and HRV signals mainly estimate correlation between power of each EEG frequency bands and HRV low frequency (LF), high frequency (HF) power bands and their ratio (LF/HF). The signals are often recorded during sleep to study correlation during sleep or just to ensure no influence on a subject from outside. In [4] delta EEG showed inverse correlations with LF \( r = -0.44; P < 0.001 \) and LF/HF \( r = -0.4; P < 0.001 \) it suggests that sympathetic nervous activities became decreased with sleep deepening and increased with sleep lightening. It compares to [29], in which the results shown that during quiet sleep (QS), LF/HF was significantly and negatively correlated with delta power of EEG \( (0.5 – 4.0 \text{ Hz}) \), whereas mean RR interval and HF were not. It is concluded that during QS, cardiac sympathetic regulation is negatively related to the depth of sleep, although vagal regulation is not.

In the paper [19] overnight profiles of interbeat autocorrelation coefficients and of EEG mean frequency were found to be related with highly significant cross-correlation coefficients ranging between 0.216 and 0.638. The variations in heart rate variability preceded changes in brain activity by 1-2 min. These results demonstrate that beat to beat heart rate variability and EEG activity are closely linked during sleep in normal man [19]. Study [12] is well consistent with this result and showed that all electroencephalographic power bands are linked to normalized high frequency; modifications in cardiac vagal activity show predominantly parallel changes and precede changes in delta band by a phase shift corresponding to a lead of 125 min [12]. Such findings can lead to practical application in identification of sleep stages using only HRV. It was found in [8] that ultradian 80-120 min rhythm in the LF/(LF+HF) ratio, with high levels during rapid eye movement (REM) sleep and low levels during slow wave sleep (SWS). During sleep stage 2 there was a progressive decrease in the transition from REM sleep to SWS, and an abrupt increase from SWS to REM sleep. These oscillations were significantly coupled in a ‘mirror-image’ to the overnight oscillations in delta wave activity, which reflect sleep deepening and lightening. Cardiac changes preceded EEG changes by about 5 min. These findings demonstrate the existence of an inverse coupling between oscillations in delta wave activity and heart rate variability. They indicate a non-uniformity in sleep stage 2 that underlies ultradian sleep regulation [8]. Results in study [1] have shown that in normal group, delta EEG which often prevails in deep sleep was inversely correlated with LFnu and HFnu and positively correlated with HFnu suggesting a decrease in sympathetic activity and an increase in parasympathetic activity. The study elucidated a significant correlation between cardiac activity and EEG frequency bands particularly in delta, beta and sigma in sleep apnoea group. Further studies using non-linear methods for EEG and ECG feature extraction is required to verify this association [1].

All the overviewed papers showed significant correlation between EEG and HRV power bands during sleep. Currently the possible use of such findings is the estimation of sleep quality and sleep stages using only HRV signal and possible diagnosis tool to diagnose sleeping disorders. But, as emphasized in the latter paper the use of non-linear methods for EEG and ECG feature extraction and more complex connectivity estimators may reveal more impressive results.

### 3.2. Spectral coherence

Spectral coherence is a statistic that estimates the relation between two signals. It is widely used to estimate the power transfer between input and output of a linear system. It can be used to estimate the causality between the input and output if the system function is linear and the signals are ergodic. Spurious results can be obtained when transfer function is nonlinear, it is probably the case in EEG-HRV analysis of connectivity. In the study [12] the coherence among the measured ECG signal and the measured EEG signal at different heart rates and different respiratory rates was calculated. The maximum coherence is 0.4650 near the frequency 0.1 Hz and the minimum coherence is 0.0045 near the frequency 0.42 Hz. The maximum coherence found between the ECG and EEG near the frequency 1 Hz [25].

In the study [12] heart rate and sleep electroencephalogram signals were recorded in 8 healthy young men. Spectral analysis was applied to electrocardiogram and electroencephalogram recordings. Spectral components of RR intervals were studied across sleep stages. The cross-spectrum maximum was determined as well as coherencies, gains and phase shifts between normalized high frequency of RR intervals and all electroencephalographic frequency bands, calculated over the first 3 non-rapid eye movement(NREM)-rapid eye movement (REM) sleep cycles. RR intervals increased from awake to NREM and decreased during REM. Normalized low frequency decreased from awake to NREM and increased during REM while normalized high frequency evolved conversely. Coherencies between normal-
ized high frequency and power spectra were high for all bands.

The latter paper showed not only the possibility of determining sleep stage using only HRV signal but that all electroencephalographic power bands are linked to normalized high frequency of HRV signal and that modifications in cardiac vagal activity precede changes in delta band [12].

3.3. Mutual information

Mutual information (MI) (of two random variables) is a quantity that measures the mutual dependence of the two random variables. High mutual information indicates a large reduction in uncertainty; low mutual information indicates a small reduction; and zero mutual information between two random variables means the variables are independent. The paper [2] presents the pilot study which assessed the multivariate analysis of EEG and ECG activity in the healthy and sleep apnoea patients during different sleep stages. The results indicated that the brain is dependent more on the heart electrical activity during different sleep stages in the healthy and sleep apnoea. This might suggest that the information that flows from the heart, actually modulates the brain electrical activity or simply that heart drives the brain activity [2]. Also the calculation of MI could be useful in diagnostics because studies in the epileptic and Alzheimer patients have recorded a lower value of MI compared to the healthy ones [2].

3.4. Transfer entropy

Transfer entropy measures the amount of directed transfer of information between two random processes. Transfer entropy is able to detect the directed exchange of information between two systems. Unlike MI, it is designed to ignore static correlations due to the common history or common input signals. Most prominent applications include multivariate analysis of time series and the study of spatially extended systems [24]. It was found in [9] that the symbolic transfer entropy about wake and the first stage of non-rapid eye movement sleep reflect on the changes of sleep stage. And it was confirmed by T-test and multi-samples experiments. The symbolic transfer entropy can apply into automatic sleep stage classification.

3.5. Synchronization likelihood

The synchronization likelihood (SL) is defined in [26] as a measure which describes how strongly particular channel at specific time is synchronized to all the other channels. In the special case of two time series the time-dependent MI is related to the synchronization likelihood. Difference between MI and SL is that the latter is normalized and the former not. Also, the computation of SL is more straightforward for data sets with more than two channels. In the study [10] was performed a synchronization likelihood computation between the different sleep bands and the HFnu band of HRV. Results corresponding to the synchronization of the $\delta$ band and the HFnu of HRV indicate a clear sign of interdependency as the synchronization likelihood is greater than the value of $P_{ref} = 0.05$ corresponding to totally uncorrelated systems. It was reached the synchronization likelihood values ranging from 0.116 and 0.235. Similar results were observed for the other sleep bands [10].

In the paper [11] the synchronizations between the high frequency component of heart rate variability and all sleep power bands exhibited robust fluctuations characterized by self-similar temporal behavior of $1/f$ noise type. No effects of sleep apnea–hypopnea syndrome were observed in these synchronizations. Sleep apnea–hypopnea syndrome does not affect the interdependence between the high frequency component of heart rate variability and all sleep power bands as measured by synchronization likelihood [11].

4. Discussion

As it was shown the connectivity analysis between EEG and HRV signals as representative of CNS and CVS interconnection estimation is multifold. Thorough study was conducted to find linear connections between power of each frequency band of EEG and HRV signal. Apparently the interconnection between such complex systems cannot be absolutely linear, so, even if the results of linear analysis may seem usable, it is evident (as elementary elements of brain activity, i.e. neuron firing, are governed by non-linear law) that the appropriate non-linear method of interconnection analysis should be found to estimate complex connectivity between the systems. From this point of view the following diagram (Fig. 1) may be used in further research to make rigorous assumptions of interconnections between CNS and CVS and to visualize current state of the art in this field.

Also, such characteristic of HRV analysis as symbolic dynamics may be suitable for the quantification of cardiac time series complexity independent of its magnitude, and is a potentially promising tool for short-term heart rate variability assessment. The symbolic dynamics concept allows a simplified description of the system dynamics with a limited set of symbols. Consecutive values of heart rate time series/their differences are encoded according
to some transformation rules into a few symbols of a certain alphabet. Subsequently, the dynamics of that symbol string are quantified, providing information about various qualitative aspects of heart dynamics [28].

![Diagram of interconnection assessment between CNS and CVS](image)

**Fig. 1. The algorithm of interconnection assessment between CNS and CVS**

The non-linear methods that were described in this paper were not carefully put to test precisely the EEG-HRV connectivity neither was done the comparison between regarded methods. After reviewing all the above mentioned papers we can determine that further research should be directed into examination of non-linear connectivity between these signals, methods for non-linear connectivity assessment and comparison of their performance.

**Conclusions**

After analysis of the state-of-art papers on the topic of this paper it can be affirmed that there is definite interconnection between central nervous and cardiovascular systems. But the peculiar method of assessment of this interconnection that can take into account the underlying manner of this connection is yet to be determined. It also should be asymmetrical regarding the driver-response relations between CNS and CVS, because the way of regulation is a very important aspect of the connection. All the reviewed papers deal mainly with certain method without making a comparison with adjacent ones, neither the performance comparison is done as well. The novelty of the research lays in the overall state of art review of the interconnection estimation between central nervous and cardiovascular systems and in the brief comparison of the results that are obtained in the field of study.

Hence, as a result of the present paper the following unsettled problems are chosen as a further direction of the research:

- Determination of time delay which may be present between corresponding actions in connected systems.
- Utilizing raw power density in frequency bands as input parameters to connectivity estimators as well as more complex nonlinear parameters.
- Selection of appropriate features. It should be determined which combination of signal parameters would reflect better the interconnections.
- Comparison of all regarded methods that are used in connectivity estimation on the same signal database.
- Comparison between linear/nonlinear parameters (in various combinations).
- Development of new connectivity measures specifically adapted for EEG and HRV signals.

**References**

Аналіз взаємозв’язку між центральною нервовою та серцево-судинними системами

В роботі розглянуто взаємозв’язок між центральною нервовою та серцево-судинними системами. Описані існуючі методи оцінки зв’язку між сигналами варіабельності серцевого ритму і електроенцефалограми людини: кореляція, когерентність, взаємна інформація, ентропія передачі, їмовірність синхронізації. Найбільш перспективними напрямами визнано дослідження нелінійного взаємозв’язку між розглянутими системами, розгляд методів оцінки нелінійного зв’язку між сигналами ЕКГ та сигналами варіабельності серцевого ритму та їх порівняння. Визначені шляхи покращення існуючих підходів до даної задачі та напрямки подальших досліджень. Бібл. 29, рис. 1.

Ключові слова: ЕКГ, варіабельність, ЕЕГ, кореляція, ентропія передачі.

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