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Directional Couplings Between Electroencephalogram and Interbeat Intervals Signals in Awake State and Different Stages of Sleep

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Abstract— **Purpose of the work is to identify the directional coupling between the structures of the brain and the autonomic control of the heart rate variability, to analyze the changes in these coupling in sleep and in wakefulness. Infra-slow oscillations of the electroencephalograms potential and low-frequency components (0.04-0.15 Hz) of the interbeat intervals signal where analyzed using a sensitive method for identifying the directional coupling. The technique, based on modeling the dynamics of instantaneous phases of oscillations, made it possible to reveal the presence and quantify the directional couplings between the structures of the brain and the autonomic control of the heart rate variability. It was shown that the coupling coefficients in the frequency band of 0.04-0.15 Hz (associated mainly with sympathetic control of blood circulation), on average, decrease with falling asleep. We have also shown the asymmetry of coupling. At the same time, stronger connections were revealed in the direction from the autonomic control of the heart rate variability to the brain structures than in the opposite direction. It has been shown that the strength of such couplings decreases with increasing of sleep depth.**

I. INTRODUCTION

The normal functioning of the human body requires the coordinated work of a huge number of complex nonlinear systems of high dimension: cardiovascular, respiration, autonomic control, cortex activity etc. This is provided by a complex connectivity network between different systems [1].

On the one hand, the study of the coupling structure between such systems has great fundamental physiological importance. This provides information about the structure of body systems and their collective dynamics [2]. On the other hand its allow to create new methods of personalized medical diagnostics and therapy [3].

The objects of this study are the processes in the brain and the process of the heart rate variability (HRV), it reflects their oscillatory dynamics in the electroencephalogram (EEG) and the interbeat intervals (RR-intervals) signals. Research is of great interest are so called Low Frequency-band (LF-band) 0.04-0.15 Hz associated mainly with sympathetic control of blood circulation for the human [3, 4]. The RR-intervals signal reflects the process of the HRV. Human EEG shows oscillations with frequencies less than 0.5 Hz (delta-band). There is evidence that such infra-slow potential oscillations may reflect the activity of autonomic control centers [5-7]. It was shown the synchronization of the EEG infra-slow oscillations on the occipital leads and the extracellular records of neurons in the reticular formation of the brain stem [7, 8]. The results of these works show that EEG infra-slow oscillations are the reflection of processes in the brain associated with autonomic nervous system activity [7, 9] and regulation of the heart and arterial pressure [8, 10].In works [11, 12] special active experiments and analysis of LF- and HF-band of HRV oscillations and infra-slow EEG oscillations using nonlinear dynamics methods made it possible to demonstrate the synchronization between the studied processes.

We have recently shown the possibility of applying the phase dynamics modeling method to analyze the directional couplings between some elements of cardiovascular system [13-16].

The process of autonomic control is known flexibly reacts to going from wakefulness to sleep and to changes in sleep phases. Settle down into the rapid-eye-movement (REM) sleep phase leads to a decrease in the tone of parasympathetic regulation and activation of sympathetic regulation. The opposite effect is observed during the NREM sleep phase [17-21].

So the aim was to study the directional couplings between the brain structures and the autonomic control loop of the HRV from the analysis of time series of infra-slow EEG oscillations and low-frequency components (0.04-0.15 Hz) of RR-intervals signals in the awake state, REM-sleep and non-REM (NREM, slow-wave) sleep.

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II. DATA

We used simultaneous signals from parietal leads C3, C4 and electrocardiogram (ECG) of 5 healthy male aged 52±10 years (mean ± standard deviation) with an average level of physical activity from the SIESTA database [22, 23]. We have used 9 segments of slow-wave sleep S3 (hereinafter referred to as NREM), 9 segments of REM sleep, and 5 segments of wakefulness. Sleep stage marking was carried out by the recommendations of Rachtsaffen and Kales [24]. The duration of each stage was 20 minutes.

An equidistant sequence of RR-intervals was extracted from the ECG using the recommendations [3].

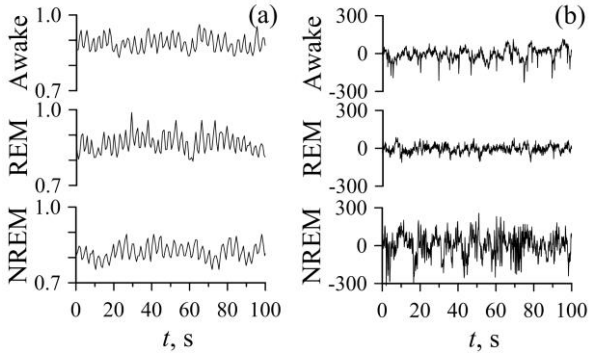

Figure 1. Typical shapes of the experimental signals: (a) – time series of RR-intervals, (b) – time series of EEG signal. The RR-interval signal is measured in seconds; EEG is measured in microvolts (uV).

III. METHOD

We calculate the strength of the directional coupling between the studied processes using the simultaneous oscillations from EEG and RR-intervals in LF-band. We used the method that was proposed in [25, 26] and adopted for the analysis of the studied processes in [13].

Assessment of the directional coupling between the studied processes begins with the identification of instantaneous phases of the signals in the corresponding frequency ranges.

To identify the phases, we filter EEG and RR signals in LF-band (band-pass filter 0.04-0.15 Hz). Then, we resampled the signals to 16 Hz and calculated the instantaneous phases for RR-intervals – $\{\varphi_x(t_1), \dots, \varphi_x(t_N)\}$ and EEG – $\{\varphi_y(t_1), \dots, \varphi_y(t_N)\}$, ($t_i = i\Delta t$, Δt – sampling interval, N – sample length) using the Hilbert transform [27].

The dynamics of the phase signal was approximated using the first-order phase oscillators [28]:

$$d\varphi_x(t)/dt = w_x + K_x\left(\varphi_x(t), \varphi_y\left(t - \Delta_{y\to x}\right)\right) + \xi_x(t), \quad (1)$$

where x, y - first and second systems ($x \neq y$), w_x - parameters that determine the angular vibration frequencies, K_x - defines the coupling between the x and y, $\Delta_{y\to x}$ - delay between the systems, $\xi_x(t)$ - white zero-mean noise. Then we create the model of the phase increment over the period of τ seconds:

$$\varphi_x(t+\tau) - \varphi_x(t) = \\ = F_x\left(\varphi_x(t), \varphi_y(t-\Delta), \bar{\boldsymbol{a}}_x\right) + \eta_x(t), \quad (2)$$

where F_x is the third-order trigonometric polynomial function, $\bar{\boldsymbol{a}}_x$ - the vector of 4 its coefficients, Δ - trial delay, $\eta_x(t)$ – model residuals. From time series we estimated the coefficients $\bar{\boldsymbol{a}}_x$ using the least squares method. We then calculated the coupling strengths in direction from *y* to *x* for a trial time-delay of Δ:

$$G^2_{xy}(\Delta) = \iint_0^{2\pi} \left(\frac{\partial F_x(\Delta)}{\partial \varphi_y}\right)^2 d\varphi_x d\varphi_y \quad (3)$$

We used τ equal to one characteristic oscillation period in the considered frequency range. The trial delay Δ was varied from 0 to 10 s. The coupling coefficient is normalized to the variance of the instantaneous phase signal of the acting system. Thus, for example, the values of $G^2_{xy}(\Delta)$ characterize what fraction of the variance of the signal phase oscillations RR-intervals can be described using the values of the signal phase oscillations EEG.

The same methods and parameters were used when calculating the coupling strengths in the opposite direction from RR-intervals and to EEG $G^2_{yx}(\Delta)$.

If the assessment of the coupling strength $G^2_{yx}(\Delta)$>0, then we considered that the oscillations RR-intervals affects the infra-slow EEG oscillations on the corresponding frequency band. If $G^2_{xy}(\Delta)$>0, the coupling was diagnosed with the opposite direction. If both coefficients were larger than zero, then we diagnosed the bidirectional coupling.

To provide non-biased estimates of coupling coefficients, we used continuous recording segments with a duration of 20 minutes (about 120 characteristic periods).

IV. RESULTS

Typical examples of RR-interval signals and an EEG signal of one subject in the studied stages are shown in Fig. 1 (a, b).

In this study, we calculated the coefficients of $G^2_{xy}(\Delta)$ and $G^2_{yx}(\Delta)$ in the LF-bands for EEG and RR in the stages of awake, REM sleep and the slow-wave NREM sleep.

Figure 2 shows the examples of dependencies of the coefficients $G^2_{xy}(\Delta)$ and $G^2_{yx}(\Delta)$ from the trial delay Δ.

Figure 2a shows an example of coupling coefficients between the studied signals in the LF-band for awake state for one of the subjects. The maximum coupling coefficient reaches a value of 0.07 (Fig. 2, thick line) for direction from RR-intervals to the EEG signal. For the opposite direction

coupling coefficient reaches a value of 0.03 (Fig. 2, thin line). Thus this example shows a more prominent effect of RR-intervals to EEG coupling in the LF-band than for opposite direction. Figure 2b,c shows an example of the analysis of directional couplings for REM and NREM sleep.

Significant fluctuations in the magnitude of the delay Δ are observed when analyzing relatively short signals of complex shape [29].

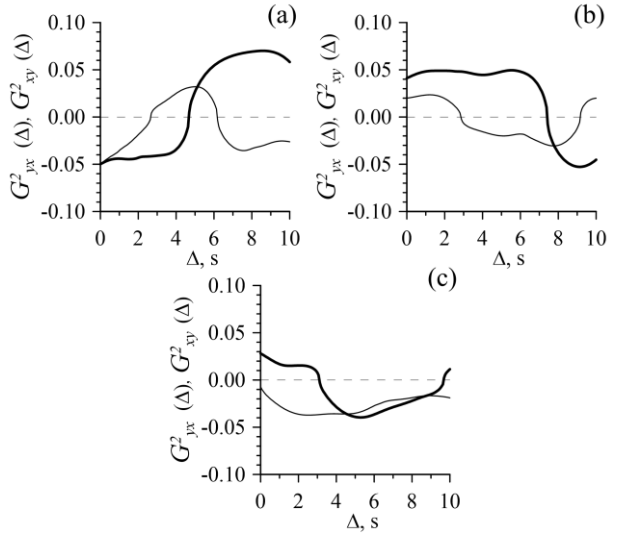

Figure 2. Dependences between the coupling coefficients $G^2_{xy}(\Delta)$ and $G^2_{yx}(\Delta)$ and the trial delay Δ for RR-intervals and EEG signals in the LF-band for the subject # 1: (a) - awake state, (b) – REM sleep, (c) - NREM sleep. The thick line for the coupling direction from RR-intervals to EEG signal ($G^2_{yx}(\Delta)$). The thin line for the opposite direction ($G^2_{xy}(\Delta)$). The dotted line is the zero level.

Therefore, in order to reduce the dimensionality of the problem, we calculated the maximum value of the directional coupling strengths from EEG to RR-intervals $\max G^2_{xy} = max\ G^2_{xy}(\Delta)$ and from RR-intervals to EEG signal: $\max G^2_{yx} = max\ G^2_{yx}(\Delta)$ when iterating over values of trial delay. Further, we used only the maximum values of the coefficients: $\max G^2_{xy}$ and $\max G^2_{yx}$ and estimated the mean and standard deviation.

Figure 3 shows the indices $\max G^2_{xy}$ and $\max G^2_{yx}$ averaged over the experimental ensemble for the awake state, NREM sleep and REM sleep stages in the LF-band.

The analysis of indices for the whole experimental ensemble made it possible to reveal the difference in the properties of directional coupling between the studied signals in sleep and awake state.

For awake state the priority coupling direction from RR-intervals to EEG signals was revealed (Fig. 3, Awake). In this case, the mean values $\max G^2_{yx}$ are significantly higher than $\max G^2_{xy}$. For NREM and REM sleep $\max G^2_{xy}$ and $\max G^2_{yx}$ demonstrate rather symmetric coupling in both directions (Fig. 3, NREM).

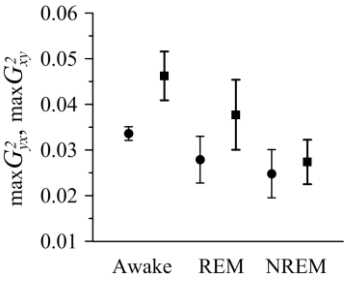

Figure 3. Indices $\max G^2_{xy}$ and $\max G^2_{yx}$ averaged over the experimental ensemble. Circles are for the direction of coupling from EEG to RR-intervals ($\max G^2_{xy}$), squares are for the direction of coupling from RR-intervals to EEG ($\max G^2_{yx}$). The whiskers corresponds to the standard error values.

Figure 3 shows the bidirectional coupling between EEG and RR-intervals for the awake state and different sleep stages. Figure 3 shows a decrease of indices while going from wakefulness to sleep. The mean values in the LF-band for awake state are $\max G^2_{xy}$ 0.034±0.002 (mean±standard error) and $\max G^2_{yx}$ 0.046±0.005 (Fig. 3, Awake). These values are significantly higher than for the NREM sleep (0.025±0.005 and 0.027±0.004) (Fig. 3, NREM). The REM sleep stage has an intermediate position in values $\max G^2_{xy}$ and $\max G^2_{yx}$ between the NREM sleep and wakefulness (0.028±0.005 and 0.038±0.008) (Fig. 3, REM).

V. Discussion

In [5, 8], authors emphasized that infra-slow EEG oscillations are most likely not the intrinsic low-frequency oscillations of the neurons of the brain cortex, but a projection onto the cortex of the activity of the underlying structures involved in the processes of autonomic control. Known studies [6, 7] describe the results of experiments with animals and suggest the correlation between infra-slow EEG oscillations and processes of autonomic control. The obtained results support the known hypothesis about the interaction of structures located in the brain stem with elements of autonomic control of the HRV [30]. The fact of the presence of such interaction is also noted in known studies [20]. The outcomes indicate the possible ways that ensure the coupling between processes in the cerebral cortex with autonomic control of the HRV

Significant fluctuations in the estimates of the delay time of couplings are due to the non-stationarity of the studied systems, noise influence, as well as the limited duration of available time series. The latter is a known problem when using similar methods [26]. It requires special studies and in this case does not allow interpreting the information on delays of couplings, forcing to be limited only to the analysis of the maximum values of the coupling coefficients.

The ratio in the values of the directional coupling coefficients (the degree of asymmetry) looks like a sensitive indicator that depends on the physiological state of the subject. Awake state is characterized by asymmetry of

coupling between the studied processes in the LF-band. Stages of sleep represent more symmetrical coupling. The obtained result potentially can be used to solve the task of classifying the sleep stages.

On average, there is a decrease in the coupling coefficients as the transition from the waking state to deeper sleep. This has the potential to be important in assessing the depth of anesthesia.

We used only 5 subjects in the study, the records of which were available to us. This limits the generality of the results obtained. More reliable estimates of the calculated of the directional coupling coefficients require an increase in the experimental sample.

VI. Conclusion

In this study, the technique for identifying the directional coupling based on modeling the dynamics of instantaneous phases of oscillations made it possible to identify and quantitatively characterize the interaction between the structures of the brain and the autonomic control loop of HRV.

During the analysis of time series of infra-slow EEG oscillations and RR-intervals of healthy subjects (SIESTA database), it was shown that the coupling coefficients, on average, decrease as they fall asleep. It was also shown that the coupling asymmetry (the ratio between the values of the directional coupling coefficients) in the LF-frequency band depends on the physiological state of the subjects and differs in awake state, REM sleep and S3 NREM sleep stages. The results obtained make it possible to better understand the features of the interaction of the higher nervous centers and elements of autonomic control of HRV. The results are seems promising for the development of methods for classifying the sleep stages.

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Conflict of interest

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Klinikum der Philipps-UniversitätMarburg, Germany. The study participants, all above age of 18 years, provided written informed consent to participate in the study.

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