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Articles

Frequency analysis based on synchrosqueezed wavelet transforms of brain and heart rhythms in cases of cerebral vascular pathology

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Introduction: *The analysis of interrelationships between the bioelectric activity of the brain and heart is one of the topical issues in modern neuroscience. Special attention of researchers in this area is attracted by the study of these interrelationships in cases of cerebral vascular pathology.* ***Purpose:*** *The use of synchrosqueezed wavelet transforms to measure the relationship between the rhythms of the brain and heart in cases of vascular pathology of varying severity before and during hyperventilation load.* ***Results:*** *The analysis of instantaneous frequencies has been carried out in the low-frequency components of an electroencephalogram and the RR interval time series extracted from the electrocardiogram of patients with vascular pathology of varying severity before and during hyperventilation. The research shows that the time when a correlation between instantaneous frequencies of the infra-slow oscillations of an electroencephalogram and the RR interval time series occurs is related to the degree of severity of cerebral vascular pathology. It has been found that the greater the severity of the vascular pathology of the brain, the faster a correlation occurs between instantaneous frequencies in the low-frequency components of an electroencephalogram and heart rate variability.* ***Practical relevance:*** *The discovered peculiarities of the frequency interrelationships between the rhythms of the brain and heart during hyperventilation may be useful for the search of neurophysiological correlates of the degree of severity of cerebral vascular pathology.*

Keywords *— electroencephalogram, heart rate variability, synchrosqueezed wavelet transform..*

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Introduction

When diagnosing violations of the functional state of the brain associated with vascular pathology, the analysis of the bioelectrical activity of the brain in the form of an electroencephalogram (EEG) is usually used. Vascular pathology of the brain is associated with a slowly progressive lack of blood supply to the brain, leading to increasing diffuse structural changes and impaired cognitive functions of the brain [1–6].

The importance of early diagnosis of such disorders necessitates the search for neurophysiological correlates of cerebral vascular pathology of varying severity [2, 6]. At the same time, the importance of studying infra-slow EEG oscillations, is noted, since it is assumed that these oscillations, in contrast to the higher-frequency components of the EEG, are associated with the regulation of the rhythms of respiration and heart [7]. In this regard, the simultaneous analysis of the bioelectrical activity of the brain under conditions of forced breathing (functional load in the form of a hyperventilation test) and an electrocardiogram (ECG) of the heart with subsequent analysis of the dynamics of frequencies can facilitate the search for markers of vascular pathology of the brain.

The difference in the frequency ranges of the EEG and ECG leads to the need to use the preliminary allocation of a single range in these signals. In this case, the nonstationarity of the EEG and ECG leads to the fact that it is not entirely correct to apply the spectral Fourier analysis. Instead, it is more correct to use the method of calculating instantaneous frequencies based on the wavelet transform of the signal [8, 9]. This method is widely used to detect synchronization between the rhythms of the cardiovascular and respiratory systems [10–15]. The works [16–18] show the importance of assessing the degree of synchronization for studying the functional state of autonomic regulation of blood circulation for persons with cardiovascular diseases, assessing personal cardiovascular risk and optimizing drug therapy.

In contrast to the rhythms of the cardiovascular and respiratory systems, the bioelectric activity of the brain, recorded from the surface of the head in the form of an EEG, is usually very noisy. To improve the efficiency of extracting the instantaneous frequency and phase from experimental data with a high level of noise, it is better to use the synchrosqueezed wavelet transform method [19]. In works [20, 21], this method was applied to identify instantaneous phases and frequencies for subsequent analysis of phase synchronization between rhythmic brain photostimulation and the response to it in the form of an EEG, and data were obtained that make it possible to distinguish the synchronization parameters in two groups of people with chronically high blood pressure. with and without mild cognitive impairment. It has been shown that these disorders correlate with a longer duration of phase synchronization and a shift in brain responses to a lower frequency range as compared to the excitation frequency [20, 21].

The purpose of this work is to use synchrosqueezed wavelet transform to assess the ratio of instantaneous frequencies in the low-frequency components of the EEG (in the infra-slow oscillations range) and the time sequence of time intervals between two consecutive R peaks extracted from ECG patterns in patients with vascular pathology of varying severity before and during hyperventilation load.

Experimental data and methods of their analysis

We analyzed EEG and ECG records obtained from 9 healthy subjects (women aged 31 to 43 years) and 15 patients (women aged 56 to 65 years) with vascular pathology associated with vegetative-vascular dystonia (group I, consisting of 8 people) and associated with vertebrobasilar insufficiency, which developed as a result of cervical osteochondrosis (group II, consisting of 7 people). Data provided by the St. Petersburg Neurological Clinic, study approved by the local ethics committee.

Vegetative-vascular dystonia is a syndrome presented in the form of various disorders of the autonomic function associated with a disorder of neurogenic regulation and arising due to an imbalance in the tonic activity of the sympathetic and parasympathetic divisions of the autonomic nervous system. This syndrome is manifested by violations of the functional state of the nervous system.

Vertebrobasilar insufficiency is a deterioration in the functioning of the brain due to a weakening of blood flow in the basilar and vertebral arteries. Vertebrobasilar insufficiency can develop in any age group, and late diagnosis combined with late treatment increases the likelihood of stroke. It is believed that the manifestations of vascular pathology of the brain are more pronounced in patients with vertebrobasilar insufficiency caused by cervical osteochondrosis than in patients with vegetative-vascular dystonia [22].

EEG and ECG signals were recorded simultaneously at rest and under the influence of functional load (hyperventilation) on a 21-channel electroencephalograph company “Mizar-EEG” (Russia, St. Petersburg). Hyperventilation load consisted of the use of spontaneous enhanced breathing during EEG recording for 3 min. The depth of inhalation and exhalation was to be maximum, and the frequency was about 20 breaths per minute.

The duration of each recording was 6 min. Three measurements were taken with each subject on different days. The sampling rate is 512 Hz. Artifacts caused by eye blinking or motor movements were previously removed by a neurophysiologist. Mathematical transformation of signals using the method of independent components was not carried out.

For EEG analysis, we used data in the occipital lobes of the brain (O_1-, O_z- and O_2-leads), where the bioelectric activity of the brain was most pronounced in all records.

Figure 1, *a–d* shows short fragments of typical experimental EEG and ECG recordings for a healthy subject and a patient with vascular pathology.

To extract the sequence of RR intervals from the ECG signal, that is, the time intervals between two consecutive R peaks, we used a wavelet transform with a sym4 basic wavelet resembling a QRS complex in shape [22]. Then the non-equidistant sequence of RR intervals was approximated by cubic splines and sampled at a frequency of 256 Hz. The resulting equidistant sequence determines the so-called heart rate variability (HRV). The EEG sequence was also resampled at a frequency of 256 Hz.

An example of a fragment of the initial ECG and the pattern obtained after the wavelet reconstruction of this fragment is shown in Fig. 2, *a–c*.

To analyze the frequencies of the infra-slow oscillations range, the original EEG records were filtered with a bandwidth of 0.04–0.45 Hz. The choice of this bandwidth is due to the fact that it is in this range that it is possible to compare with heart rate variability.

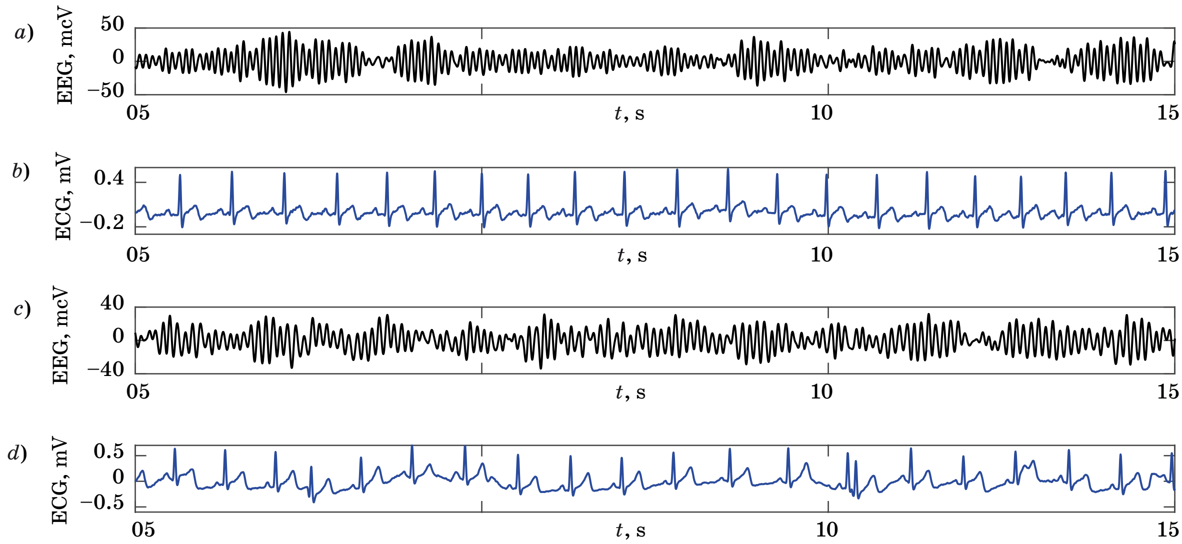
To assess the ratio of instantaneous frequencies of EEG patterns in the infra-slow oscillations range and in the HRV sequence, we used the synchrosqueezed wavelet transform method [19].

In this work, as a wavelet function, we used the Morlet wavelet, which is usually used for continuous wavelet transform of a signal:

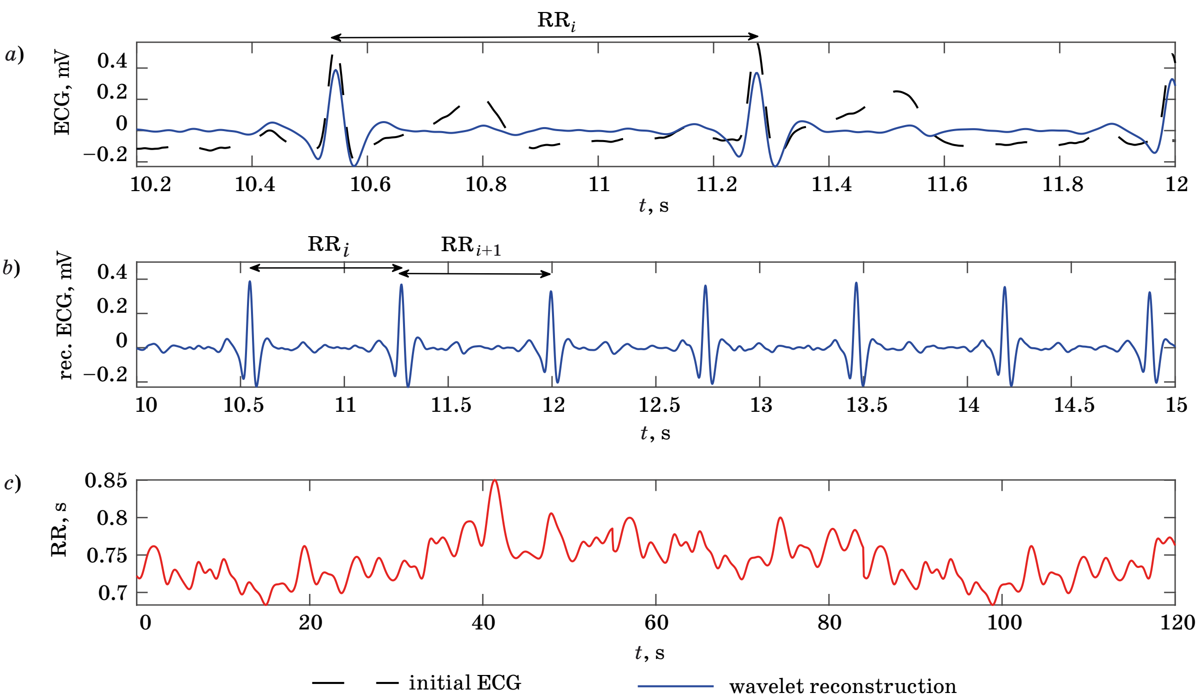
$$\Psi(t-b)/a) = = (1/a)\exp[i\omega_0((t-b)/a]\exp(-0.5((t-b)/a)^2), \quad (1)$$

which at the value of the wavelet parameter $\omega_0 = 2\pi f_0$, $f_0 = 1$, provides a simple relationship between the scale a of the wavelet transform and the real frequency f of the analyzed signal [8]:

$$f = \left(\left(\omega_0 + \sqrt{2+\omega_0^2}\right)/4\pi a\right) \approx 1/a. \quad (2)$$



■ ***Fig. 1.*** Examples of EEG and ECG fragments for a healthy subject (a, b) and a patient with vascular pathology (c, d)



■ ***Fig. 2.*** Fragment of the initial ECG and pattern after wavelet reconstruction (a, b) and sequence of RR intervals (c)

The continuous wavelet-transform (CWT) of the signal $s(t)$ for the wavelet function $\psi(t)$ is defined by the formula

$$W_s(a, b) = \frac{1}{a}\int_{-\infty}^{+\infty} s(t)\overline{\psi}\left(\frac{t-b}{a}\right)\mathrm{d}t, \qquad (3)$$

where a and b are scale and time shift variables; $\psi((t-b)/a)$ is the wavelet function obtained from the mother wavelet $\psi(t)$ by scaling and time shift, the symbol means complex conjugation [8].

The synchrosqueezed wavelet-transform (SWT) of the signal $s(t)$ is specified as follows [19]:

$$T_s(\omega_l, b) = \frac{1}{\Delta\omega}\sum_{a_k} W_s(a_k, b)a^{-3/2}\Delta a_k,$$

$$a_k : \left|\omega(a_k, b) - \omega_l\right| \le \Delta\omega / 2, \qquad (4)$$

where ω_l — l^{th} discrete circular frequency; a_k — k^{th} discrete scale and $\Delta a_k = a_k - a_{k-1}$.

In the spectrum of synchrosqueezed wavelet transform, each signal component is represented by a time sequence of maxima of SWT coefficients, the so-called ridge curve [9]:

$$\omega_r(b) = \arg\max\left|T_s(\omega_l, b)\right|,$$
$$\omega_l \in \left[\omega_r(b) - \Delta\omega/2,\ \omega_r(b) + \Delta\omega/2\right]. \quad (5)$$

Extraction of the ridge from the SWT signal $s(t)$ can be reduced to solving the problem of conditional search optimization among all curves $\omega_r(t_0)$ of the one that maximizes the SWT modulus along the ridge [23]. This is equivalent to minimizing the penalty function [23] of the following form:

$$P(\omega_r) = -\int\left|T_s(\omega_r(b), b)\right|^2 \mathrm{d}b +$$
$$+ 0.01\int\left[\left(\frac{\mathrm{d}\omega_r(b)}{\mathrm{d}b}\right)^2 + \left(\frac{\mathrm{d}^2\omega_r(b)}{\mathrm{d}^2 b}\right)^2\right]\mathrm{d}b. \quad (6)$$

Based on the obtained crests $\omega_r(b)$ the instantaneous frequency $f_s(b)$ can be calculated by the formula [9]

$$fs(b) = \omega_r(b/2\pi). \quad (7)$$

By applying SWT to the EEG and HRV signals, we estimated their instantaneous frequencies and then calculated the instantaneous frequency ratio $f_s(b)/f_p$.

The integral calculated below

$$E_{SW}(f) = \int_{t_1}^{t_2}\left|T_s(f, b)\right|^2 \mathrm{d}b \quad (8)$$

determines the time-averaged distribution of the synchrosqueezed wavelet spectrum energy over frequencies at a given time interval $[t_1, t_2]$.

The time (Δt_{cor}) of the appearance of the correlation of the instantaneous frequencies of the infra-slow oscillations range of the EEG and HRV was determined as the time interval during which, after the start of the hyperpolarization test, the ratio was established:

$$0.95 \le f_{\text{EEG}}/\ f_{\text{HRV}} \le 1.05. \quad (9)$$

To compare the mean Δt_{cor} values obtained for different groups of subjects, one-way ANOVA was used. Statistically significant differences between groups were determined on the basis of $p < 0.017$ values due to the fact that the number of groups is $k = 3$, $n = k(k - 1)/2 = 3$, $1 - 0.95^{1/n} = 0.017$.

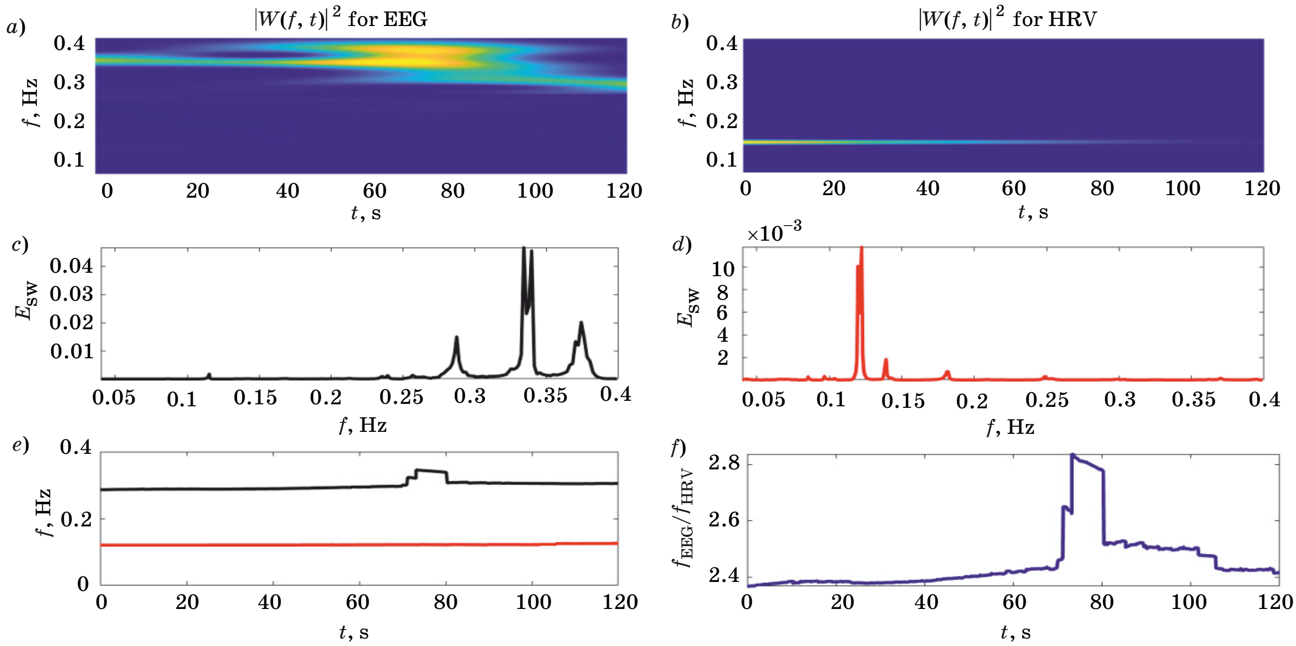
Results

Due to the fact that no significant differences were found for all subjects for the right and left leads O_1 and O_2, this work will present the results obtained only for the central lead O_z.

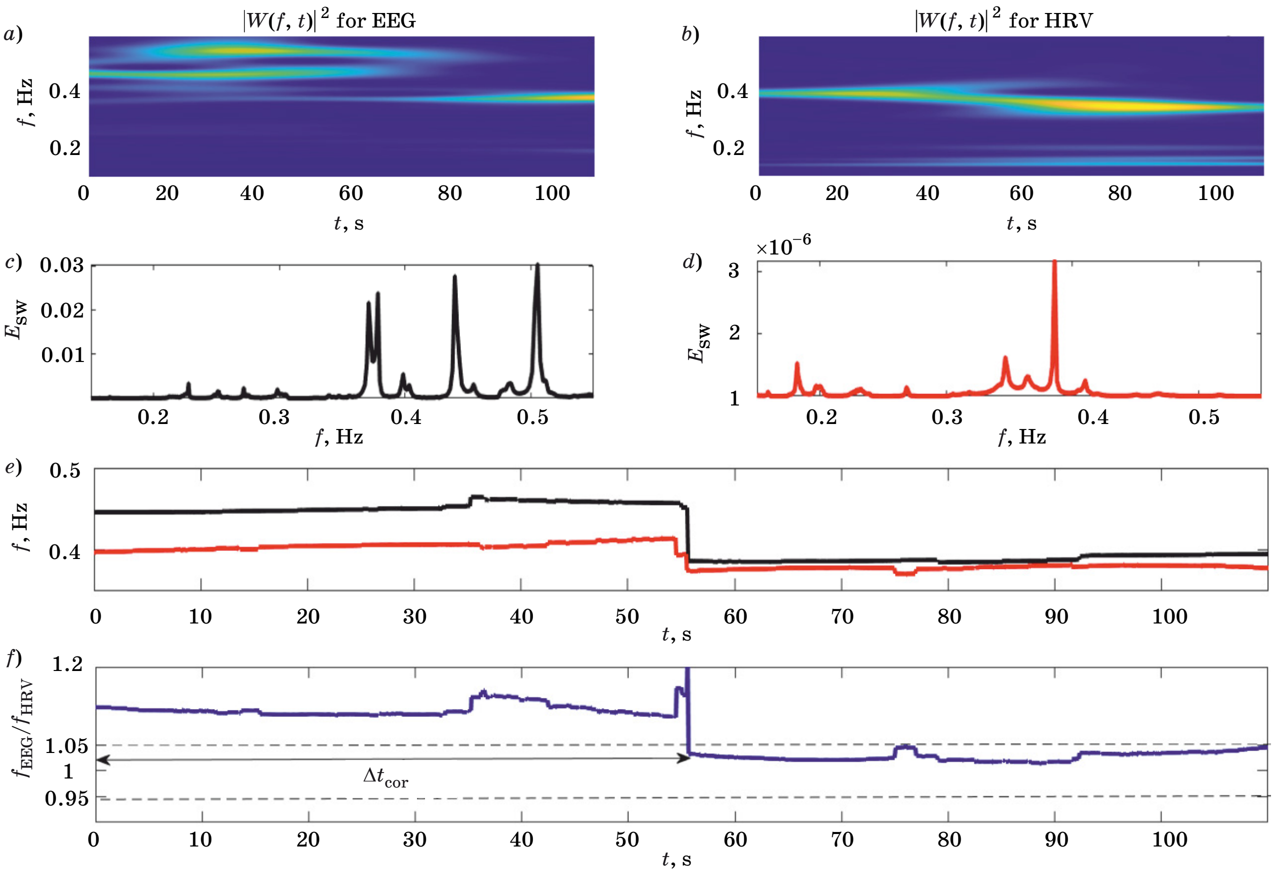
Figure 3 demonstrates an example of the absence of relationships between the instantaneous frequencies of the EEG infra-slow oscillations range and HRV. This example was obtained for patient A with vascular disease from group I before the hyperventilation test. The projection of the wavelet surface $(t, f, |W_s(f, t)|^2)$ onto the plane (t, f), obtained by the CWT (Continuous Wavelet Transform) method for the EEG (Fig. 3, *a*), has frequency bands that do not coincide with the band on the projection of the wavelet surface for HRV (Fig. 3, *b*). Time-averaged energy distributions $E_{\text{SW}}(f)$ of synchrosqueezed wavelet spectra of EEG and HRV in frequencies have maxima at frequencies of 0.34 and 0.12 Hz for EEG and for HRV, respectively (Fig. 3, *c*, *d*). The ridges extracted from the SWT are shown in Fig. 3, *e*. The ratio of instantaneous frequencies $f_{\text{EEG}}/f_{\text{HRV}}$ calculated on the basis of these ridges exceeds the value 2 (Fig. 3, *f*).

Figure 4 shows that, in contrast to the absence of relationships between the instantaneous frequencies of the infra-slow oscillations range in the background EEG and HRV for patient A, correlations arise between the instantaneous frequencies of the EEG and HRV during hyperventilation load. The projections of the wavelet surfaces $(t, f, |W_s(f, t)|^2)$ onto the plane (t, f) for EEG and HRV have bands that coincide near a frequency of 0.4 Hz (Fig. 4 *a*, *b*). Time-averaged energy distributions $E_{\text{SW}}(f)$ of synchrosqueezed wavelet spectra have well-defined maxima at frequencies of 0.39, 0.46, and 0.51 Hz for EEG and 0.39 Hz for HRV, respectively (Fig. 4 *c*, *d*). The ridges isolated from the SWT spectra approach each other as much as possible at a frequency of 0.39 Hz 55 s after the onset of hyperventilation (Fig. 4, *e*). Thus, the time interval during which the ratio of instantaneous frequencies $f_{\text{EEG}}/f_{\text{HRV}}$ becomes equal to 1±0.05 (Fig. 4, *f*), is 55 s. So, for patient A, the time of occurrence of the correlation between the instantaneous frequencies of the EEG infra-slow oscillations range and HRV during the hyperventilation load $\Delta t_{\text{cor}} = 55$ s.

Patient B from group II is also characterized by the presence of relationships between the instantaneous frequencies of the infra-slow oscillations range in the EEG and HRV during hyperventilation (Fig. 5). The coincidence of the bands in the projections of the wavelet surfaces $(t, f, |W_s(f, t)|^2)$ onto the plane (t, f) for EEG and for HRV occurs near a frequency of 0.28 Hz (Fig. 5 *a*, *b*). Time-averaged energy distributions $E_{\text{SW}}(f)$ of synchrosqueezed wavelet spectra for EEG and HRV have well-defined maxi-



■ ***Fig. 3.*** Projections of the wavelet surface $(t, f, |W_s(f, t)|^2)$ onto the plane (t, f), obtained by the CWT method for EEG and HRV before hyperventilation (a, c); time-averaged distribution of the synchrosqueezed wavelet spectrum energy over frequencies $|T_s(f, b)|^2$ (b, d); extracted ridges (e) and instantaneous frequency ratio (f) for patient A from group I



■ ***Fig. 4.*** Projections of the wavelet surface $(t, f, |W_s(f, t)|^2)$ onto the plane (t, f), obtained by the CWT method for EEG and HRV during hyperventilation(a, b); time-averaged distribution of the synchrosqueezed wavelet spectrum energy over frequencies $|T_s(f, b)|^2$ (c, d); extracted ridges (e) and instantaneous frequency ratio (f) for patient A from group I ma at a frequency of 0.28 Hz (Fig. 5 *c*, *d*). The ridges isolated from the SWT spectra approach each other as much as possible at this frequency of 0.28 Hz 42 s after the onset of hyperventilation (Fig. 5, *e*). Thus, for patient B, the time for the appearance of a correlation between the instantaneous frequencies of the infra-slow oscillations EEG and HRV during hyperventilation is less than for patient A and is Δt_{cor} = 42 s (Fig. 5, *f*).

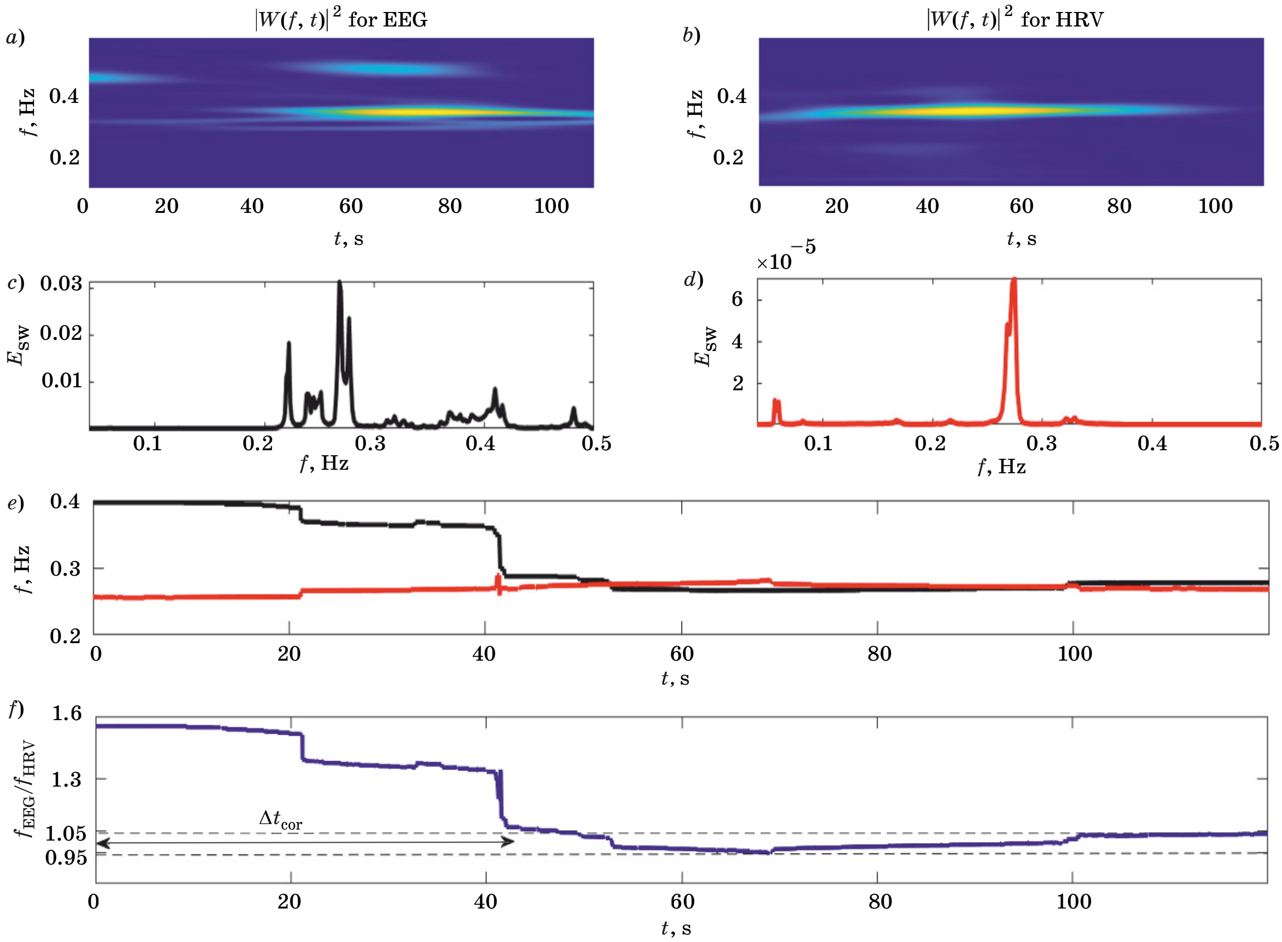
Based on the data obtained, it can be seen that the correlation between the instantaneous frequencies of the infraslow EEG rhythm and heart rate variability after hyperventilation exercise in patients with vertebrobasilar insufficiency, which developed as a result of cervical osteochondrosis, occurs faster than in patients with vegetovascular dystonia. Since physiologically vertebrobasilar insufficiency is a more dangerous pathology for the brain than vegetative-vascular dystonia (which can be both a somatic disease and a mental disorder), it can be argued that the more pronounced the vascular pathology of the brain, the faster the correlation between instantaneous frequencies of EEG infraslow rhythm and heart rate variability.

Average values of instantaneous frequencies of EEG and HRV patterns before and during hyperventilation for analyzed groups are presented in Table.

The data in Table indicate that there is no correlation between the instantaneous frequencies of the low-frequency infra-slow oscillations range of background EEG and HRV patterns for both groups with vascular pathology and for the control group of healthy subjects.

The mean f_{EEG} values before hyperventilation are (0.35±0.05) Hz for patients from group II. The mean f_{HRV} values before hyperventilation are less and equal to (0.12±0.03) Hz for patients from group I and (0.18 ± 0.04) Hz for patients from group II.

During hyperventilation, the mean f_{EEG} values increased and were equal to (0.43±0.07) Hz for patients from group I and (0.31±0.05) Hz for patients from group II, (0.35±0.05) Hz for the control group. The mean f_{HRV} values also increased and were



■ ***Fig. 5.*** Projections of the wavelet surface (t, f, $|W_s(f, t)|^2$) onto the plane (t, f), obtained by the CWT method for EEG and HRV during hyperventilation (*a*, *b*); time-averaged distribution of the synchrosqueezed wavelet spectrum energy over frequencies $|T_s(f, b)|^2$ (*c*, *d*). Extracted ridges (*e*) and instantaneous frequency ratio (*f*) for patient B from group II

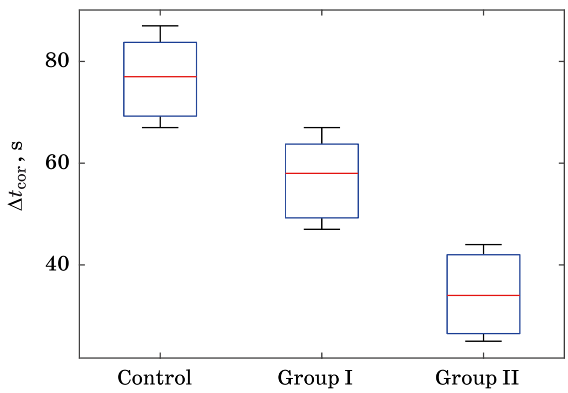
■ Average values of instantaneous EEG and HRV frequencies before and during hyperventilation for different groups

Subjects	f_{EEG}, Hz	f_{HRV}, Hz
Before hyperventilation		
Control group (N = 9/9)	0.19±0.04	0.10±0.03
Group I (N = 8/8)	0.29±0.05	0.12±0.03
Group II (N = 7/7)	0.35±0.05	0.18±0.04
During hyperventilation		
Control group (N = 9/9)	0.35±0.05	0.30±0.06
Group I (N = 8/8)	0.43±0.07	0.38±0.06
Group II (N = 7/7)	0.31±0.05	0.23±0.04

equal, respectively, to (0.38±0.06) Hz for patients from group I and (0.23±0.04) Hz for patients from group II.

The results of one-way analysis of variance for comparing the mean values of Δt_{cor} values for different groups of subjects are shown in Fig. 6. This figura demonstrates the difference in the mean times of occurrence of the correlation between the instantaneous frequencies of the infra-slow oscillations range EEG and HRV during hyperventilation.

Large differences in the center lines (medians of the sample values Δt_{cor}), indicate significant differences in the group means. The statistics obtained by Fisher's F-criterion $F = 48.5$, exceeds the critical value $F_{2.18} = 3.5$. Values 2 and 18 correspond to the number of $k = 3$ tested groups, the number of 7 averaged values in each group, and the total number of observations $N = 7 \times 3 = 21$, and therefore $k - 1 = 2$, $N - k = 18$. The significance level of the Fisher criterion, i.e. the maximum probability of mistakenly rejecting the null hypothesis of equality of means, when it is true, is close to zero ($p = 0.0002$). Therefore, the ANOVA test used showed significant differences between the mean Δt_{cor} values for patients from the three test groups.



■ ***Fig. 6.*** One-way ANOVA results for comparing the mean Δt_{cor} values for the analyzed groups

Thus, the correlation observed for both analyzed groups between instantaneous frequencies of the EEG infra-slow oscillations range and HRV patterns under hyperventilation load is statistically significantly different in the time of occurrence of such a correlation. The mean Δt_{cor} value is maximal (Δt_{cor} = 76.4 ± 8.3) for the control group, the mean Δt_{cor} value is lower in patients with vascular pathology associated with vertebrobasilar insufficiency (Δt_{cor} = 34.3 ± 8.0, group II), compared with the mean value Δt_{cor} = 56.4 ± 8.1, obtained for patients with less severity of vascular pathology associated with vegetative-vascular dystonia (group I).

Thus, for the first time, using nonlinear methods for analyzing non-stationary signals, statistically significant differences in the time of occurrence of the correlation of instantaneous frequencies of the infra-slow oscillations range of electroencephalograms and heart rate variability after the start of the hyperpolarization test were revealed in patients with varying degrees of severity of vascular pathology. The results obtained support the hypothesis that heart rate variability is in a complex dynamic interaction with the rhythms of the electrical activity of the brain [7, 24].

Our results are to some extent consistent with the results of [25, 26], which assessed the presence of synchronization between infra-slow rhythms in the EEG and signals in photoplethysmograms in healthy men during functional tests with a linearly increasing (over 30 min) respiratory rate. In work [24], areas of phase and frequency synchronization were revealed between respiration, which increases linearly in frequency, and infra-slow rhythms in the occipital EEG derivations, as well as respiration and low-frequency rhythms in photoplethysmograms. It was shown in [26] that for different areas of the brain, infraslow oscillations can have a different order of synchronization with respiration.

It is quite probable that in our results the appearance of relationships between the instantaneous frequencies of the infraslow EEG rhythm and heart rate variability after hyperventilation exercise may be associated with an increase in the amplitude of respiration and linear leakage of the respiration signal with characteristic frequencies of 0.15–0.50 Hz into the signal of RR intervals and EEG.

Significantly shorter analyzed records did not allow us to detect areas of phase synchronization between the EEG and HRV rhythms, and therefore the search for phase synchronization will be continued for longer records and studying the peculiarities of the interaction of the circulatory regulation system, the respiration process, and neuronal activity of the brain.

Conclusion

Analysis of instantaneous frequencies in the low-frequency components of the EEG and the time sequence of RR intervals extracted from the ECG, carried out before and after hyperventilation for two groups of subjects with vascular pathology of varying severity, showed that a decrease in the time of occurrence of a correlation between instantaneous frequencies of the EEG infra-slow oscillations range and HRV is associated with the degree of cerebrovascular disease. The greater the severity of the vascular pathology of the brain, the faster there is a correlation between the instantaneous frequencies of the EEG infra-slow oscillations range and heart rate variability.

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Частотный анализ на основе синхросжатого вейвлет-преобразования ритмов мозга и сердца при сосудистой патологии мозга

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Введение: анализ взаимосвязей биоэлектрической активности мозга и сердца является одним из актуальных вопросов в современной нейронауке. Особое внимание исследователей в данной области привлекает изучение этих взаимосвязей при сосудистой патологии мозга. **Цель исследования:** опыт применения синхросжатого вейвлет-преобразования для оценки связи между ритмами мозга и сердца при сосудистой патологии различной степени тяжести до и во время гипервентиляционной нагрузки. **Результаты:** проведен анализ мгновенных частот в низкочастотных составляющих электроэнцефаллограммы и временной последовательности RR-интервалов, извлеченных из электрокардиограммы у пациентов с сосудистой патологией различной степени тяжести до и во время гипервентиляционной нагрузки. Показано, что время возникновения корреляции мгновенных частот сверхмедленных ритмов электроэнцефаллограммы и временной последовательности RR-интервалов связано со степенью сосудистой патологии головного мозга. Обнаружено, что чем больше выраженность сосудистой патологии мозга, тем быстрее возникает корреляция между мгновенными частотами в низкочастотных составляющих электроэнцефалограммы и вариабельности сердечного ритма. **Практическая значимость:** выявленные особенности частотных взаимосвязей ритмов мозга и сердца во время гипервентиляционной нагрузки могут быть полезны при поиске нейрофизиологических коррелят степени тяжести сосудистой патологии головного мозга.

Ключевые слова — электроэнцефалограмма, вариабельность сердечного ритма, синхросжатое вейвлет-преобразование.

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