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Synchronization analysis of time series obtained from anesthetized rats during painful action*

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Abstract. The *purpose* of this work is to determine the possibility of detecting changes in the relationships between such physiological rhythms as the activity of neurons in the reticular formation of the medulla oblongata, fluctuations in the blood pressure and respiration in anesthetized rats before and during the development of a pathological state associated with painful colorectal distension. This stretch mimics the pain localized in the lower abdomen in patients with irritable bowel syndrome and it is accompanied by responses of the brain neurons, fluctuations in the blood pressure and respiration. The analysis of changes in the relationships of these rhythms consisted in identifying phase synchronization between the time series of the variability of neuronal activity intervals and the variability of blood pressure intervals at the respiratory rate before and during pain exposure. *Methods.* To solve this problem, the synchrosqueezed wavelet transform method was applied, which makes it possible to effectively calculate the instantaneous frequencies and phases of non-stationary signals. As indicators of synchronization, we used the values of the index and the duration of phase synchronization as a time interval during which the value of the synchronization index is close to 1. *Results.* It has been established that the pain effect provides an adjustment of the frequency of the neuronal activity variability and the occurrence of synchronization between this activity and the blood pressure variability at the respiratory rate or causes an adjustment of the frequency of the blood pressure variability and the occurrence of synchronization between the blood pressure variability and the respiratory rhythm. It was found that the pain effect increases the duration of phase synchronization between the variability of the blood pressure and the respiratory rhythm or reduces the duration of phase synchronization between the variability of neuronal activity and the respiratory rhythm. *Conclusion.* The effect of painful colorectal distension on changes in the parameters of phase synchronization between physiological rhythms in anesthetized rats was studied in detail.

Keywords: synchrosqueezed wavelet transform, phase synchronization, physiological rhythms.

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Introduction

The study of transitions from an unsynchronized state to a synchronized state is of particular interest for assessing the degree of control impairment in various physical [1–4] and biological [5–11] systems. For example, the analysis of synchronization of electrical activity in different loci of the brain allows identifying the epileptic focus in patients with focal epilepsy [12]. The analysis of synchronization of the slow component of the heart rate and vascular tone oscillations in studies of simultaneous recordings of electrocardiograms and photoplethysmograms is important for determining the functional state of the autonomic regulation of blood circulation in patients with cardiovascular diseases [13–16]. Disturbances in the cardiovascular system after acute myocardial infarction can cause a decrease in the duration of synchronization between heart rate and blood pressure oscillations [15, 16]. A decrease in the influence of control mechanisms from the nervous system can lead to a change in the duration of synchronization between the respiratory and cardiovascular systems [17, 18]. Thus, pathological conditions of the body can change the synchronized interactions of various physiological systems.

In this paper, abdominal pain accompanying functional diseases of the human gastrointestinal tract, the most common of which is irritable bowel syndrome, is considered as a pathological condition. It is assumed that the development of this syndrome is based on the interaction of a stress factor and disturbances in intestinal motor activity due to dysregulation in the neural networks that ensure the conduction and control of nociceptive signals in the gastrointestinal tract–brain–gastrointestinal tract system [19, 20].

To study the mechanisms of abdominal pain development in physiology, experiments on anesthetized animals are used, in which nociceptive colorectal distension imitates pain localized in the lower abdomen in patients with irritable bowel syndrome [19]. This distension is accompanied in anesthetized rats by reactions of neurons in the visceral nuclei of the brainstem, as well as contractions of the abdominal muscles and changes in heart rate and blood pressure [19, 20].

In this regard, it seems relevant to analyze the formation of reactions of various physiological systems, i.e. changes in the rhythms of the cardiovascular, respiratory and nervous systems to the occurrence of abdominal pain. This involves clarifying the interaction between the variability of blood pressure, the rhythm of breathing and the variability of neuronal activity of the brain during pain exposure. To study such interaction, it is important to set the task of analyzing possible synchronization between the patterns of these physiological rhythms, assessing the parameters of this synchronization before and during pain exposure.

For this purpose, various approaches related to the analysis of frequency and phase synchronization of non-stationary signals can be used. For example, the analytical signal method, including the Hilbert transform [21], is used to identify synchronization between the rhythms of the cardiovascular and respiratory systems, i.e. to study the interaction between the respiratory rhythm, blood pressure fluctuations, and the variability of the R–R intervals of the main heart rhythm [22–25].

Another approach is to extract instantaneous frequencies and phases based on the wavelet transform of the signal [26]. This approach is used to analyze neural connections between different brain regions [27] and to identify synchronization between breathing rhythm and heart rate variability [6–9].

To improve the efficiency of extracting instantaneous frequencies and phases from non-stationary experimental data with a high noise level, there is the synchrosqueezed wavelet transform method [28]. This method is also used to estimate the dynamics of respiration based on the heart rhythm [29, 30]. In works [10, 11] this method is used to identify instantaneous phases and frequencies for subsequent analysis of phase synchronization between rhythmic photostimulation and brain responses in the form of electroencephalograms in patients with hypertension and initial manifestations of mild cognitive impairment and without such

manifestations. As a result, data were obtained that allow us to conclude that synchronization parameters can serve as neurophysiological markers of cognitive impairment.

Thus, methods for assessing the degree of phase synchronization allow us to assess the degree of impairment of physiological systems in various pathologies.

The aim of this work is to identify phase synchronization between the variability of arterial blood pressure and the variability of intervals of neuronal activity of neurons of the ventrolateral reticular formation of the medulla oblongata of anesthetized rats at the respiratory rate before and during painful colorectal distension.

1. Methodology

1.1. Experimental data. The analyzed data were provided by the Laboratory of Cortico-Visceral Physiology of the Pavlov Institute of Physiology of the Russian Academy of Sciences and contained fluctuations in arterial pressure, respiration, and neuronal activity of 10 rats anesthetized with urethane (1.5 mg/kg) before and during pain stimulation. These data were registered in accordance with the Directive of the Council of the European Communities (86/609/EEC) and the requirements of the Commission for the Care and Use of Laboratory Animals at the Pavlov Institute of Physiology of the Russian Academy of Sciences (conclusion No. 02/24 dated February 24, 2020).

Blood pressure was recorded by a pressure sensor located in a catheter installed in the femoral artery (MLT0670, ADInstruments Ltd., UK). Respiratory oscillations were defined as fluctuations in CO_2 concentration measured during inhalation and exhalation using a sensor located in the endotracheal tube (CapnoScan End-Tidal CO_2 Monitoring Modular System, USA).

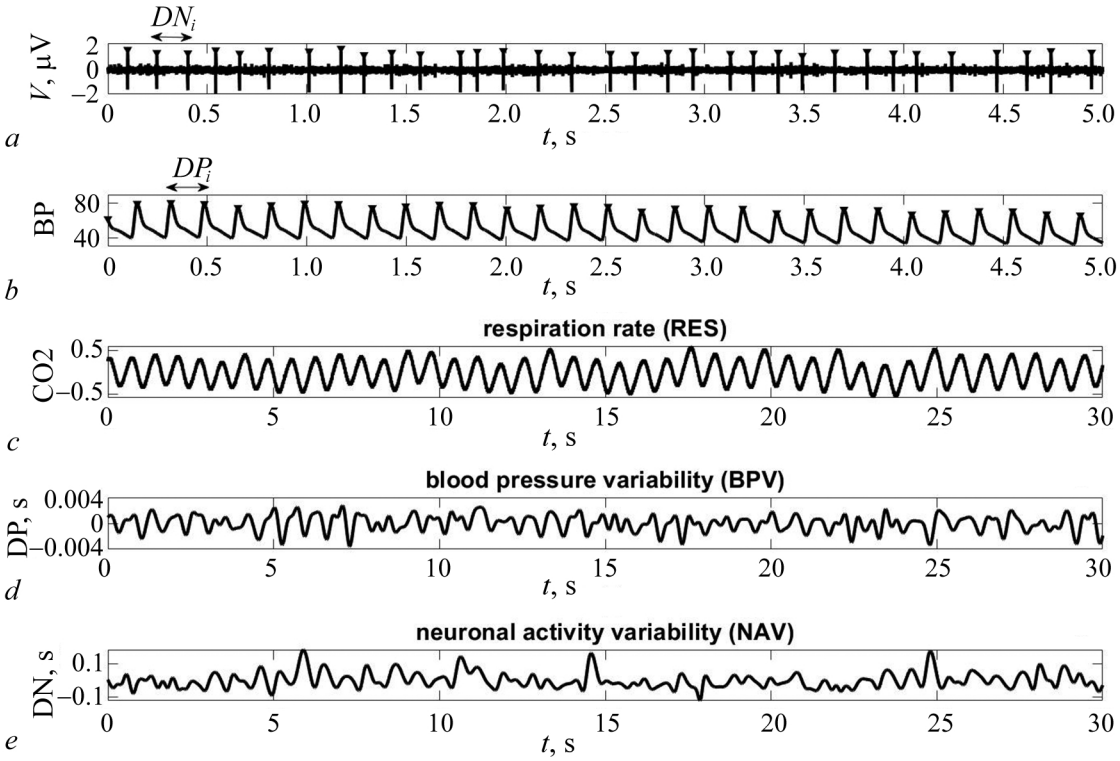

Fig 1. Fragments of the datasets: *a* — the neuronal activity; *b* — the blood pressure fluctuations; *c* — respiratory oscillations; *d* — curves of the blood pressure variability (BPV); *e* — the neuronal activity variability (NAV). Intervals DN_i и DP_i are indicated in *a* and *b*

Neuronal activity was recorded using a tungsten electrode (WPI, USA) immersed in the caudal ventrolateral reticular formation of the medulla oblongata. This was due to the fact that it is in this area of the medulla oblongata that groups of neurons responding to painful colorectal distension were found [31].

Pain stimulation meant mechanical stretching of the colorectal region of the colon with a rubber balloon for 60 seconds. The sampling frequency was 10,000 Hz.

Short fragments of experimental data on neuronal activity, blood pressure and respiration are shown in Fig. 1, *a, b, e*; selected curves of neuronal activity interval variability (NAV) and blood pressure interval variability (BPV) are shown in Fig. 1, *c, d*.

These curves contained sequences of time intervals between local maxima of the original data of neuronal activity and blood pressure. The obtained curves were approximated by cubic splines with resampling to a frequency of 1000 Hz and removal of nonlinear trends. Then we applied filtering, removing low-frequency fluctuations (less than 1 Hz) in the obtained NAV and BPV curves, to analyze the components of these curves with fundamental frequencies close to the respiratory rhythm frequency (RES).

1.2. Evaluation of the phase synchronization index. The algorithm for calculating the phase synchronization index based on the synchrosqueezed wavelet transform [28] consists of the following sequence of procedures.

1. Construction of the projection of the wavelet spectrum $\mid W_s(\omega_l, b) \mid^2$ of the analyzed signal $s(t)$ onto the plane (b, f), where

$$W_s(f, b) = f \int_{-\infty}^{+\infty} s(t)\overline{\psi(f(t-b))}dt, \tag{1}$$

f and b are frequency and time shift; the symbol $\overline{\psi(f(t-b))}$ means the complex conjugate of the wavelet function $\psi(f(t-b))$ obtained from the Morlet mother wavelet $\psi(t)$ by scaling and time shifting [26]:

$$\psi(f(t-b)) = f \exp(i\omega_0 f(t-b) \exp(-0.5 f^2 (t-b)^2. \tag{2}$$

2. Construction of the projection of the synchrosqueezed wavelet spectrum $|T_s(\omega_l, b)|^2$ onto the plane (b, f), where

$$T_s(f, b) = \frac{1}{\triangle\omega} \sum_{f_k}^{f_t} W_s(f_k, b) f^{3/2} \triangle f_k, \tag{3}$$

$\triangle f_k = f_k - f_{k-1}$, f_k satisfies the condition $\mid \omega(f_k, b) - \omega_l \mid \leqslant \triangle\omega/2$, ω_l — lth discrete circular frequency calculated according to the formula

$$\omega_l = (l/n)F_s, \quad l = 1, ..., n, \tag{4}$$

F_s — signal sampling frequency $s(t)$, n — number of scales used in constructing the wavelet spectrum, $\triangle\omega = \omega_l - \omega_{l-1} = F_s/n$.

3. Finding ridges (frequency components of a signal) by solving a conditional search optimization problem among all those curves that maximize the coefficients of the synchrosqueezed wavelet transform [26]:

$$\omega_r(b) = \arg\max \mid T_s(\omega_l, b) \mid, \tag{5}$$

$$\omega_l \in [\omega_r(b) - \triangle\omega/2, \omega_r(b) + \triangle\omega/2]\,. \tag{6}$$

4. Calculation of instantaneous phases and frequencies based on the found ridges $\omega_r(b)$ in accordance with the formulas [32]

$$f_s(b) = \omega_r(b)/2\pi, \tag{7}$$

$$\phi_s(b) = \arg \mid T_s(\omega_r, b) \mid . \tag{8}$$

5. Calculation of the ratio of instantaneous frequencies $f_{s1}(b)/f_{s2}(b)$ and the phase difference for two analyzed signals

$$\triangle\phi_{n,m}(b) = (n\phi_{s1}(b) - m\phi_{s2}(b))/2\pi, \tag{9}$$

where n and m are integers.

6. According to [6], phase synchronization of order $n : m$ is determined by the following conditions:

$$\mid \triangle\phi_{n,m}(b) - c \mid < \varepsilon_1, \tag{10}$$

$$\mid f_{s1}(b)/f_{s2}(b) - m/n \mid < \varepsilon_2, \tag{11}$$

where c is a constant and $\varepsilon_1 = 0.03$, $\varepsilon_2 = 0.03$, that is, in the case of phase synchronization, the instantaneous phase difference oscillates around a constant value c, and the value of the ratio of instantaneous frequencies $f_{s1}(b)/f_{s2}(b)$ changes near the value m/n.

The time-averaged energy propagation $E_{\mathrm{SW}}(f)$ of the synchrosqueezed wavelet transform $\mid T_s(f,b) \mid^2$ over frequency values is calculated in accordance with the formula

$$E_{\mathrm{SW}}(f) = \int_{t1}^{t2} \mid T_s(f,b) \mid^2 db. \tag{12}$$

The duration of phase synchronization $n : m$ between two time series is calculated as the time interval $\triangle t_{\mathrm{syn}}$ during which the value of the phase synchronization index, calculated according to [33],

$$\gamma_{n,m} = \left| \sum_{j=1}^{k} \exp(2\pi\triangle\phi_{n,m}(b + j\triangle b/k)) \right|, \tag{13}$$

is close to 1.

The differences between the average values of the phase synchronization duration for the two groups of data before and during pain stimulation in this work were identified using the one-way ANOVA analysis of variance. In this case, statistically significant differences between these data were determined based on $p < 0.05$, since $k = 2$, $n = k(k-1)/2 = 1$ and $1 - 0.95^{1/n} = 0.05$.

2. Results

Examples of projections of local wavelet spectra $\mid W_s(\omega_l, b) \mid^2$ onto the plane (b, f) for respiration rate (RES), blood pressure variability (BPV) and neuronal activity variability (NAV) before pain exposure are shown in Fig. 2, *a–c*.

The global wavelet spectrum, which is the time-averaged energy distribution $E_{\mathrm{SW}}(f)$ of the synchrosqeezed wavelet spectrum $\mid T_s(\omega_l, b) \mid^2$ over frequencies, for the NAV time series (Fig. 2, *f*) demonstrates the presence of many frequencies in the range from 1 to 3 Hz and the presence of a local maximum near the frequency corresponding to the maxima of the global wavelet spectra $E_{\mathrm{SW}}(f)$ for respiration rate (RES) and the BPV time series (Fig. 2, *d–f*). The global wavelet spectrum $E_{\mathrm{SW}}(f)$ for intervals of blood pressure variability has a maximum at respiration rate $f_{\mathrm{RES}} = 1.880.03Hz$ (Fig. 2, *e*), but this rate is not present in the BPV time series throughout the entire time interval (Fig. 2, *b*).

Frequency and phase synchronization between the NAV and BPV time series is absent in this example, since the ratio of instantaneous frequencies $f_{\mathrm{NAV}}/f_{\mathrm{BPV}}$ does not satisfy condition (9) (Fig. 2, *g*), the dependence of the instantaneous phase difference $\triangle\phi_{\mathrm{NAV-BPV}}$ on time does not have horizontal plateau sections (Fig. 2, *h*), and the phase synchronization index $\gamma_{\mathrm{NAV-BPV}}$ fluctuates around a value close to zero (Fig. 2, *i*).

In contrast, phase synchronization between the RES and BPV time series is found in the time intervals $[14, 26]$ s and $[40, 60]$ s. In these intervals, the ratio of instantaneous frequencies $f_{\mathrm{BPV}}/f_{\mathrm{RES}}$ is close to 1 (Fig. 2, *j*), the instantaneous phase difference $\triangle\phi_{\mathrm{BPV-RES}}$ is close to 0 (Fig. 2, *k*), and the phase synchronization index $\gamma_{\mathrm{BPV-RES}}$ fluctuates around a value close to 1 (Fig. 2, *l*).

Fig. 3 demonstrates the presence of phase synchronization intervals between the rhythms of neuronal activity variability and blood pressure variability, as well as between the respiratory rhythm and blood pressure variability in the same rat during pain exposure.

The ratio of instantaneous frequencies $f_{\mathrm{BPV}}/f_{\mathrm{RES}}$ oscillates around a value close to 1 (Fig. 3, *g*). Oscillations of the instantaneous phase difference $\triangle\phi_{\mathrm{BPV-RES}}$ occur around 0 (Fig. 3, *h*). Oscillations of the phase synchronization index $\gamma_{\mathrm{BPV-RES}}$ around 1 (Fig. 3, *i*) in the time interval [60...93.5] s. At the tenth second from the onset of pain exposure, the frequency

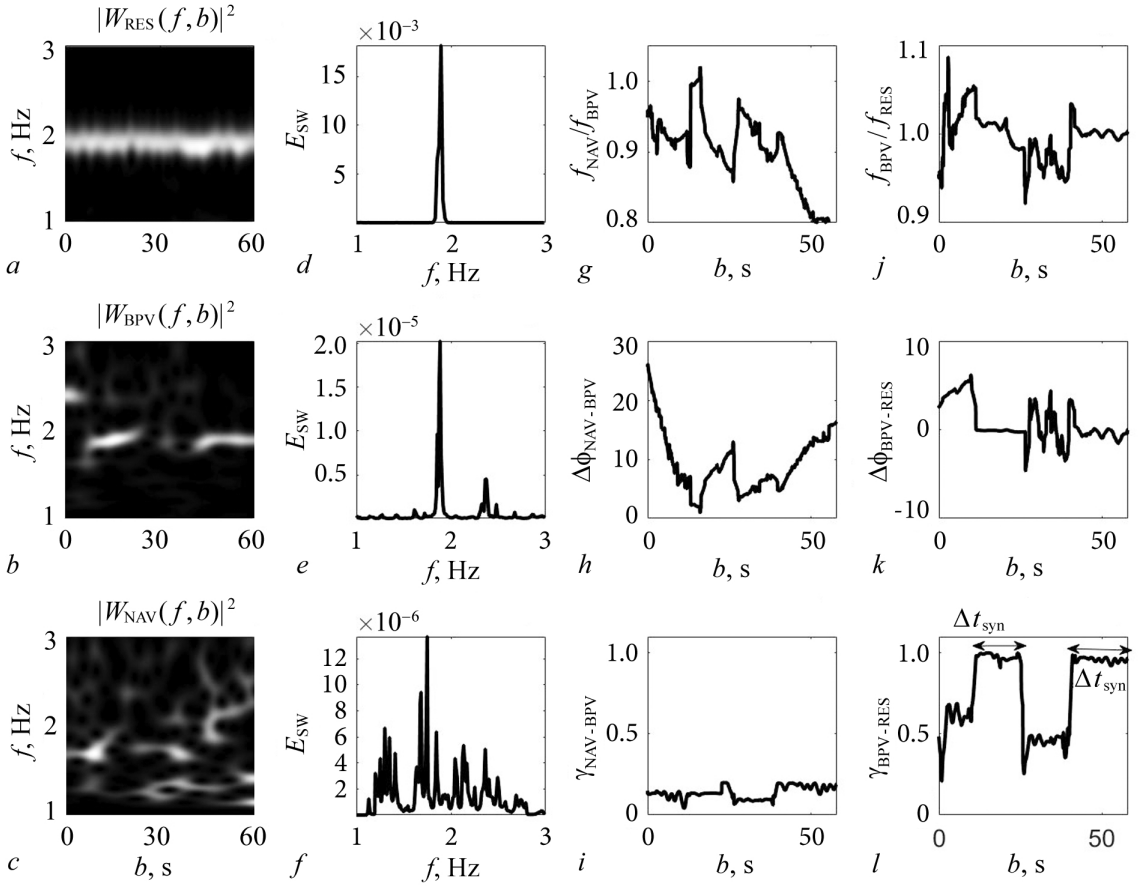

Fig 2. Examples of wavelet spectra of the RES, BPV and NAV time series and phase and frequency characteristics before the pain stimulation: *a–c* — projections of the local wavelet спектров $(b, f, |\, W_s(\omega_l, b)\,|^2)$ onto the (b, f) plane for the RES, BPV and NAV time series; *d–f* — global wavelet spectra $E_{\mathrm{SW}}(f)$ for RES, BPV, NAV; *g, j* — ratios of instantaneous frequencies $f_{\mathrm{NAV}}/f_{\mathrm{BPV}}$ and $f_{\mathrm{BPV}}/f_{\mathrm{RES}}$; *h, k* — instantaneous phase differences $\triangle\phi_{\mathrm{NAV-BPV}}$ and $\triangle\phi_{\mathrm{BPV-RES}}$; *i, l* — dependences of phase synchronization indices $\gamma_{\mathrm{NAV-BPV}}$ and $\gamma_{\mathrm{BPV-RES}}$ on time

of neuronal activity variability is adjusted and synchronization occurs between neuronal activity and blood pressure variability at a respiratory rate of f_{RES}=1.76±0.03 Hz.

In the time interval [70...97] s, the ratio of instantaneous frequencies $f_{\mathrm{NAV}}/f_{\mathrm{BPV}}$ oscillates around a value close to 1 (Fig. 3, *j*). The instantaneous phase difference $\triangle\phi_{\mathrm{NAV-BPV}}$ oscillates around 0 (Fig. 3, *k*). The phase synchronization index $\gamma_{\mathrm{NAV-BPV}}$ oscillates around 1 (Fig. 3, *l*).

The table shows the average values of the phase synchronization durations $\triangle t_{\mathrm{synBPV-RES}}$, $\triangle t_{\mathrm{synNAV-BPV}}$, $\triangle t_{\mathrm{synNAV-RES}}$ in rats before and during pain exposure.

The data in the Table show that before the pain stimulus, phase synchronization between the variability of blood pressure and the respiratory rhythm was found for the majority of experimental recordings (in seven rats out of ten). In the other three rats, synchronization between these rhythms was absent (this is indicated by the close-to-zero value of $\triangle t_{\mathrm{synBPV-RES}}$). At the same time, in these rats, phase synchronization between the variability of blood pressure and the respiratory rhythm was maintained during the pain stimulus. Synchronization between the variability of blood pressure and the variability of neuronal activity before pain stimulation was absent in these rats ($\triangle t_{\mathrm{synNAV-BPV}} = 0.5 \pm 0.3$ s). Adjustment of the frequency of neuronal activity variability ensured the emergence of phase synchronization between the variability of neuronal activity and the variability of blood pressure at the respiratory rate some time after the onset of pain exposure.

Statistically significant differences between the mean values of phase synchronization duration $\triangle t_{\mathrm{synBPV-RES}}$ for data before and during pain stimulation were determined based on $p < 0.05$. Pain exposure increased the duration of phase synchronization between blood pressure

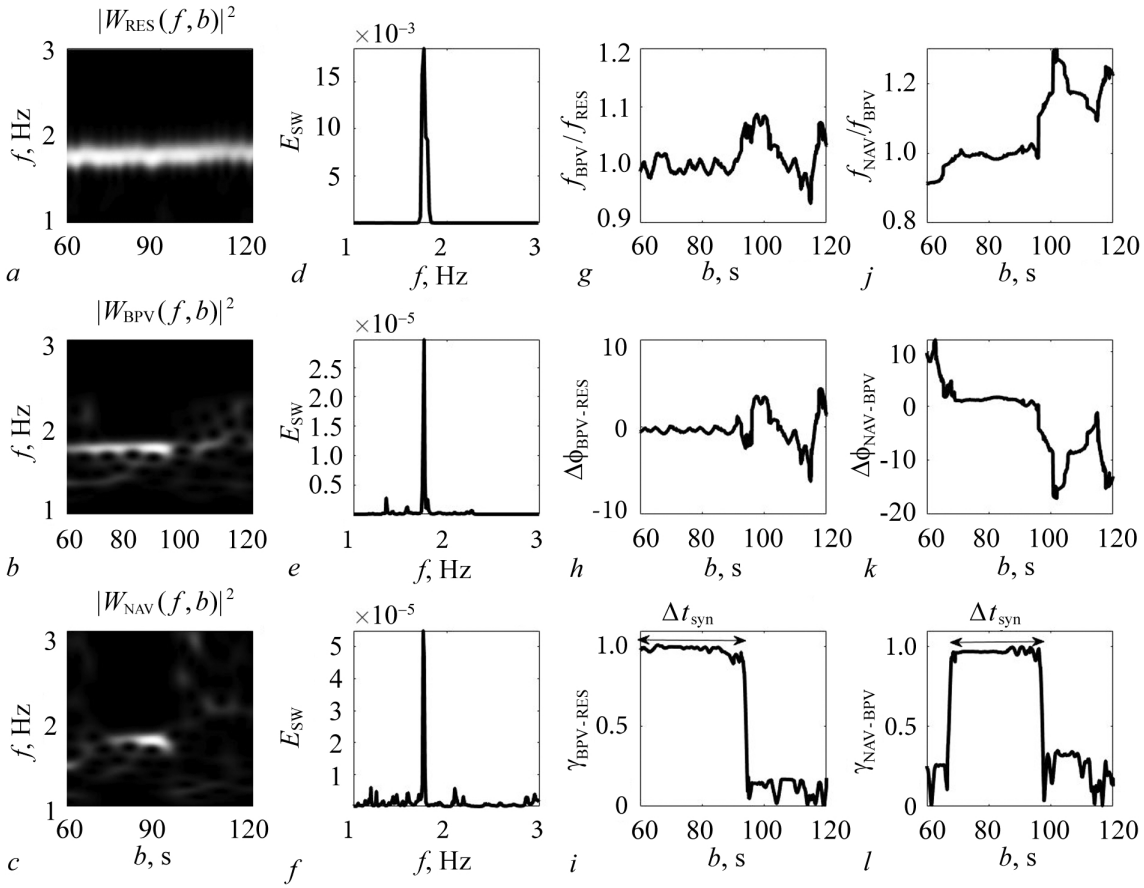

Fig 3. Examples of wavelet spectra of the RES, BPV and NAV time series and phase and frequency characteristics during the pain stimulation: *a–l* — are the same as in Fig. 2

Table. Averaged values of durations of the phase synchronization $\triangle t_{\text{synBPV}-\text{RES}}$, $\triangle t_{\text{synNAV}-\text{BPV}}$, $\triangle t_{\text{synNAV}-\text{RES}}$

rats (7/10)		
	before pain stimulation	during pain stimulation
$\triangle t_{\text{synBPV}-\text{RES}}$	33.7 ± 3.5	38.5 ± 3.9
$\triangle t_{\text{synNAV}-\text{BPV}}$	0.5 ± 0.3	34.4 ± 3.4
rats (3/10)		
	before pain stimulation	during pain stimulation
$\triangle t_{\text{synBPV}-\text{RES}}$	0.7 ± 0.3	56.2 ± 5.7
$\triangle t_{\text{synNAV}-\text{RES}}$	46.7 ± 4.9	37.8 ± 3.9

variability and respiratory rhythm ($\triangle t_{\text{synBPV}-\text{RES}} = 33.7 \pm 3.5$ s and $\triangle t_{\text{synBPV}-\text{RES}} = 38.5 \pm 3.9$ s before and after exposure, respectively).

Synchronization between the respiratory rhythm and the variability of neuronal activity intervals in the absence of pain stimulation was found in a smaller number of data (in three rats out of ten) (see Table). The analysis of variance also revealed statistically significant differences between the mean values of the duration of phase synchronization before and during pain stimulation for the values of $\triangle t_{\text{synNAV}-\text{RES}}$ at the level of $p < 0.05$.

In these cases, the pain stimulus did not disrupt the synchronization between the respiratory rhythm and the variability of neuronal activity, but decreased the duration of phase synchronization ($\triangle t_{\text{synNAV}-\text{RES}} = 46.7 \pm 4.9$ s before the stimulus and after $\triangle t_{\text{synNAV}-\text{RES}} = 37.8 \pm 3.9$ s) and caused the frequency of blood pressure variability to be adjusted to the respiratory rate, leading to synchronization between the respiratory rhythm and blood pressure variability. The average duration of phase synchronization between blood pressure variability and the respiratory rhythm for these rats was $\triangle t_{\text{synBPV}-\text{RES}} = 56.2 \pm 5.7$ s.

Conclusion

Using the synchrosqueezed wavelet transform method, we assessed the possibility of obtaining data on the occurrence of phase synchronization between various physiological rhythms in anesthetized rats before and during pain exposure.

We found that pain exposure can cause an adjustment of the frequency of variability of neuronal activity of the ventrolateral reticular formation of the medulla oblongata or the frequency of variability of arterial pressure to the respiratory rate, followed by the occurrence of phase synchronization between these time series.

Evaluation of the disappearance or occurrence of synchronization between the rhythms of various physiological systems in various pathologies of the functional state seems to be a promising means for analyzing the degree of disturbance of the regulation of these systems.

In the development of specific analgesic drugs that could influence regulation in neural networks and eliminate irritable bowel syndrome, and the need to take into account possible side effects on heart rate and blood pressure, the results obtained in the work can be used to screen new antinociceptive pharmacological drugs, to analyze their effect on interactions between physiological rhythms, in particular, on the possible suppression of synchronization between the variability of blood pressure and the variability of neuronal activity of the brain.

References

1. Ticos CM, Rosa Jr E, Pardo WB, Walkenstein JA, Monti M. Experimental real-time phase synchronization of a paced chaotic plasma discharge. Phys. Rev. Lett. 2000;85(14):2929–2932. DOI: 10.1103/PhysRevLett.85.2929.

2. DeShazer DJ, Breban R, Ott E, Roy R. Detecting phase synchronization in a chaotic laser array. Phys. Rev. Lett. 2001;87(4):044101.DOI: 10.1103/PhysRevLett.87.044101.
3. Boccaletti S, Kurths J, Osipov G, Valladares DL, Zhou CS. The synchronization of chaotic systems. Physics Reports. 2002;366(1–2):1–101. DOI: 10.1016/S0370-1573(02)00137-0.
4. Boccaletti S, Allaria E, Meucci R, Arecchi FT. Experimental characterization of the transition to phase synchronization of chaotic CO2 laser systems. Phys. Rev. Lett. 2002;89(19): 194101. DOI: 10.1103/PhysRevLett.89.194101.
5. Ponomarenko VI, Prokhorov MD, Bespyatov AB, Bodrov MB, Gridnev VI. Deriving main rhythms of the human cardiovascular system from the heartbeat time series and detecting their synchronization. Chaos, Solitons & Fractals. 2005;23(4):1429–1438. DOI: 10.1016/j.chaos.2004.06.041.
6. Bespyatov AB, Bodrov MB, Gridnev VI, Ponomarenko VI, Prokhorov MD. Experimental observation of synchronization between the rhythms of cardiovascular system. Nonlinear Phenomena in Complex Systems. 2003;6(4):885–893.
7. Hramov AE, Koronovskii AA, Ponomarenko VI, Prokhorov MD. Detecting synchronization of self-sustained oscillators by external driving with varying frequency. Phys. Rev. E. 2006;73(2):026208. DOI: 10.1103/PhysRevE.73.026208.
8. Hramov AE, Koronovskii AA, Ponomarenko VI, Prokhorov MD. Detection of synchronization from univariate data using wavelet transform. Phys. Rev. E. 2007;75(5):056207. DOI: 10.1103/PhysRevE.75.056207.
9. Moskalenko OI, Koronovskii AA, Hramov AE, Zhuravlev MO. Estimate of the degree of synchronization in the intermittent phase synchronization regime from a time series (model systems and neurophysiological data). Jetp Lett. 2016;103(8):539–543. DOI: 10.1134/S0021364016080105.
10. Dik OE, Glazov AL. Parameters of phase synchronization in electroencephalographic patterns as markers of cognitive impairment. Tech. Phys. 2021;66(4):560–570. DOI: 10.1134/S1063784221040058.
11. Dick OE, Glazov AL. Estimation of the synchronization between intermittent photic stimulation and brain response in hypertension disease by the recurrence and synchrosqueezed wavelet transform. Neurocomputing. 2021;455:163–177. DOI: 10.1016/j.neucom.2021.05.038.
12. Rangaprakash D, Pradhan N. Study of phase synchronization in multichannel seizure EEG using nonlinear recurrence measure. Biomedical Signal Processing and Control. 2014;11:114–122. DOI: 10.1016/j.bspc.2014.02.012.
13. Kiselev AR, Mironov SA, Karavaev AS, Kulminskiy DD, Skazkina VV, Borovkova EI, Shvartz VA, Ponomarenko VI, Prokhorov MD. A comprehensive assessment of cardiovascular autonomic control using photoplethysmograms recorded from the earlobe and fingers. Physiol. Meas. 2016;37(4):580–595. DOI: 10.1088/0967-3334/37/4/580.
14. Borovkova EI, Karavaev AS, Kiselev AR, Shvartz VA, Mironov SA, Ponomarenko VI, Prokhorov MD. Method for diagnostics of synchronization of 0.1 Hz rhythms of cardiovascular system autonomic regulation in real time. Annals of Arrhythmology. 2014;11(2):129–136 (in Russian). DOI: 10.15275/annaritmol.2014.2.7.
15. Hoyer D, Leder U, Hoyer H, Pompe B, Sommer M, Zwiener U. Mutual information and phase dependencies: measures of reduced nonlinear cardiorespiratory interactions after myocardial infarction. Medical Engineering & Physics. 2002;24(1):33–43. DOI: 10.1016/S1350-4533(01)00120-5.
16. Karavaev AS, Prokhorov MD, Ponomarenko VI, Kiselev AR, Gridnev VI, Ruban EI, Bezruchko BP. Synchronization of low-frequency oscillations in the human cardiovascular system. Chaos. 2009;19(3):033112. DOI: 10.1063/1.3187794.
17. Shiogai Y, Stefanovska A, McClintock PVE. Nonlinear dynamics of cardiovascular ageing.

Physics Reports. 2010;488(2–3):51–110. DOI: 10.1016/j.physrep.2009.12.003.
18. Stefanovska A, Haken H, McClintock PVE, Hožič M, Bajrović F, Ribarič S. Reversible transitions between synchronization states of the cardiorespiratory system. Phys. Rev. Lett. 2000;85(22):4831–4834. DOI: 10.1103/PhysRevLett.85.4831.
19. Lyubashina OA, Mikhalkin AA, Sivachenko IB. Supraspinal neuronal alterations promoting intestinal hyperalgesia in colitis. Integrative Physiology. 2021;2(1):71–78. DOI: 10.33910/2687-1270-2021-2-1-71-78.
20. Lyubashina OA, Sivachenko IB, Mikhalkin AA. Impaired visceral pain-related functions of the midbrain periaqueductal gray in rats with colitis. Brain Research Bulletin. 2022;182:12–25. DOI: 10.1016/j.brainresbull.2022.02.002.
21. Pikovsky A, Rosenblum M, Kurths J. Synchronization: A Universal Concept in Nonlinear Sciences. New York: Cambridge University Press; 2001. 411 p. DOI: 10.1017/CBO9780511755743.
22. Rosenblum MG, Cimponeriu L, Bezerianos A, Patzak A, Mrowka R. Identification of coupling direction: Application to cardiorespiratory interaction. Phys. Rev. E. 2002;65(4):041909. DOI: 10.1103/PhysRevE.65.041909.
23. Ponomarenko VI, Prokhorov MD, Bespyatov AB, Bodrov MB, Gridnev VI. Deriving main rhythms of the human cardiovascular system from the heartbeat time series and detecting their synchronization. Chaos, Solitons & Fractals. 2005;23(4):1429–1438. DOI: 10.1016/j.chaos.2004.06.041.
24. Kralemann B, Frühwirth M, Pikovsky A, Rosenblum M, Kenner T, Schaefer J, Moser M. In vivo cardiac phase response curve elucidates human respiratory heart rate variability. Nature Communications. 2013;4:2418. DOI: 10.1038/ncomms3418.
25. Zhang Q, Patwardhan AR, Knapp CF, Evans JM. Cardiovascular and cardiorespiratory phase synchronization in normovolemic and hypovolemic humans. European Journal of Applied Physiology. 2015;115(2):417–427. DOI: 10.1007/s00421-014-3017-4.
26. Daubechies I. Ten Lectures on Wavelets. CBMS-NSF Regional Conference Series in Applied Mathematics. Philadelphia, Pennsylvania: SIAM Publication; 1992. 369 p. DOI: 10.1137/1.9781611970104.
27. Li D, Li X, Cui D, Li ZH. Phase synchronization with harmonic wavelet transform with application to neuronal populations. Neurocomputing. 2011;74(17):3389–3403. DOI: 10.1016/j.neucom.2011.05.022.
28. Daubechies I, Lu J, Wu H-T. Synchrosqueezed wavelet transforms: An empirical mode decomposition-like tool. Applied and Computational Harmonic Analysis. 2011;30(2):243–261. DOI: 10.1016/j.acha.2010.08.002.
29. Wu H-T, Chan Y-H, Lin Y-T, Yeh Y-H. Using synchrosqueezing transform to discover breathing dynamics from ECG signals. Applied and Computational Harmonic Analysis. 2014;36(2):354–359. DOI: 10.1016/j.acha.2013.07.003.
30. Wu H-T, Lewis GF, Davila MI, Daubechies I, Porges SW. Optimizing estimates of instantaneous heart rate from pulse wave signals with the synchrosqueezing transform. Methods. Inf. Med. 2016;55(5):463–472. DOI: 10.3414/ME16-01-0026.
31. Lyubashina OA, Sivachenko IB, Sokolov AY. Differential responses of neurons in the rat caudal ventrolateral medulla to visceral and somatic noxious stimuli and their alterations in colitis. Brain Research Bulletin. 2019;152:299–310. DOI: 10.1016/j.brainresbull.2019.07.030.
32. Thakur G, Brevdo E, Fučkar NS, Wu H-T. The Synchrosqueezing algorithm for time-varying spectral analysis: Robustness properties and new paleoclimate applications. Signal Processing. 2013;93(5):1079–1094. DOI: 10.1016/j.sigpro.2012.11.029.
33. Mormann F, Lehnertz K, David P, Elger CE. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. Physica D. 2000;

144(3–4):358–369. DOI: 10.1016/S0167-2789(00)00087-7.