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Determination of the delay time of rhythmic activity associated with the nervous, respiratory and cardiovascular systems

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The task was to determine the delay time in the interaction of paired signals associated with the respiratory, cardiovascular and nervous systems using the method of modeling the phase dynamics of weakly coupled and weakly noisy periodic processes. Differences in the delay times of the influence of the respiratory rhythm on the arterial pressure variability and the influence of the arterial pressure variability on the variability of neuronal activity of the medulla oblongata of rats were revealed.

Keywords: physiological rhythms, unidirectional coupling, delay time.

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Introduction

The analysis of the relationships in the signals generated by weakly interacting systems involves clarification of not only the direction of communication between these systems [1–6], but it also requires determination of communication delays and estimation of the delay time in the impact of one system on another [4,7], since this is related to determination of the mechanism of functioning of interacting systems. The task of detection of delayed linkages in interacting systems is used in various fields of science, for example, to estimate the propagation time of a disturbance in reference chaotic oscillators [8–10], in climate systems when analyzing linkages between large-scale climatic processes [3.11], for analyzing linkages in physiological systems [5,6,12].

The delay times of interaction between 0.1 Hz rhythms of autonomic regulation of the heart rate and arterial vessel blood filling variability were determined in Ref. [5,6,13] using a method based on modeling the phase dynamics of interacting systems. These studies revealed an increase of the delay time of the influence of arterial vessel blood filling variability on heart rate variability compared with the delay time of the influence in the opposite direction for healthy subjects.

The relevance of estimation of the delay time in the direction of the link is also attributable to the fact that even it is important to determine the rate of influence of one system on another when bi-directional influence is found [5–7]. It was found in Ref. [7] that, despite the two-way linkage between subcortical vibrations and tremor vibrations of the arm of a patient with Parkinsonism, the longer delay in the influence of brain vibrations on arm vibrations indicates a more complex mechanism of brain influence on the limbs compared with the opposite influence.

The features of the interaction of oscillatory systems are sensitive markers in the pathology of systems, therefore, the analysis of the relationships between systems is considered promising for the creation of diagnostic methods [14,15]. It is indicated in Ref. [15] that the development of this field of research may lead to the development of diagnostic methods that can identify changes in the interaction of systems caused by pathological or specific factors. It was found in Ref. [16] that anesthesia suppresses the significant influence of heart rate regulation on vascular tone regulation (unidirectional relation between heart rate variability and arterial vessel blood filling variability), while general anesthesia does this to a greater extent than spinal anesthesia. The authors point out that suppressing the relationship between heart rate control and vascular tone control may be important for assessing circulatory insufficiency during surgery.

The purpose of this study is to determine the delay time of interaction of time series isolated from biological rhythms associated with the nervous, respiratory and cardiovascular systems in the form of variability in neuron activity intervals, blood pressure variability and fluctuations of respiratory rhythm during pain exposure.

Respiratory rate fluctuations (RES), curves of blood pressure variability (BPV) and neuronal activity variability (NAV) of the rat medulla oblongata, obtained in Ref. [17–19] before and during pain exposure, which is a mechanical stretching of the thick intestines with a rubber balloon. These data were used in Ref. [18] to identify phase synchronization between pairwise time series, while in Ref. [17,19] these data were used to determine the

direction of the linkages between the analyzed series and to study changes in these directions during pain exposure.

1. Method

The determination of the delay time of the influence of one system on another is based on the application of the phase dynamics model, which determines the increments of the instantaneous phases $\varphi_X(t)$ and $\varphi_Y(t)$ over the time interval τ, taking into account the delay times $\Delta_{X\to Y}$ and $\Delta_{Y\to X}$ [4]:

$$\varphi_X(t+\tau)-\varphi_X(t)=F_X(\varphi_X(t),\ \varphi_Y(t-\Delta_{Y\to X}), a_X)+\varepsilon_X(t),$$
$$\varphi_Y(t+\tau)-\varphi_Y(t)=F_Y(\varphi_Y(t),\ \varphi_X(t-\Delta_{X\to Y}), a_Y)+\varepsilon_Y(t), \quad (1)$$

where $\varepsilon_X(t)$ and $\varepsilon_Y(t)$ — Gaussian noise with zero mean.

The instantaneous phases $\varphi_X(t)$ and $\varphi_Y(t)$ were estimated in this paper using a wavelet transform with a Morlaix wavelet function [20].

Functions

$$F_X(\varphi_X(t),\ \varphi_Y(t-\Delta_{Y\to X}), a_X)$$

and

$$F_Y(\varphi_Y(t),\ \varphi_X(t-\Delta_{X\to Y}), a_Y)$$

were given by polynomials of the form [21]:

$$F_j(\varphi_X, \varphi_Y, a_j)=\sum_k a_{j,k}\exp(i(m_k\varphi_X+n_k\varphi_Y), \quad j=X, Y. \quad (2)$$

In accordance with Ref. [21,22] we used as τ the values equal to the smaller of the characteristic oscillation periods of the analyzed signals $X(t)$ and $Y(t)$, and the values of $m_k=3$, $n_k=3$.

We found the minima of the following functions for finding the coefficients a_X and a_Y:

$$S_X^2(\Delta_{X\to Y})=\frac{1}{N-\tau}\sum_{i=1}^{N-\tau}\Big((\varphi_X(t_i+\tau)-\varphi_X(t_i))-F_X(\varphi_X(t_i),\varphi_Y(t_i-\Delta_{X\to Y}),a_X)\Big)^2,$$
$$S_Y^2(\Delta_{Y\to X})=\frac{1}{N-\tau}\sum_{i=1}^{N-\tau}\Big((\varphi_Y(t_i+\tau)-\varphi_Y(t_i))-F_Y(\varphi_Y(t_i),\varphi_X(t_i-\Delta_{Y\to X}),a_Y)\Big)^2. \quad (3)$$

Based on the found functions

$$F_X(\varphi_X(t_i),\varphi_Y(t_i-\Delta_{X\to Y}),a_X),$$
$$F_Y(\varphi_Y(t_i),\varphi_X(t_i-\Delta_{Y\to X}),a_Y)$$

coefficients k_X^2 and k_Y^2 are calculated which determine the power of influence of the system Y on the system X for various values $\Delta_{Y\to X}$, and the power of influence of the system X on system Y for various values $\Delta_{X\to Y}$ [4]:

$$k_X^2=\frac{1}{2\pi^2}\int_0^{2\pi}\int_0^{2\pi}\left(\frac{\partial F_X(\varphi_X(t),\varphi_Y(t+\Delta_{Y\to X}),a_X)}{\partial\varphi_Y}\right)^2 d\varphi_X d\varphi_Y,$$
$$k_Y^2=\frac{1}{2\pi^2}\int_0^{2\pi}\int_0^{2\pi}\left(\frac{\partial F_Y(\varphi_Y(t),\varphi_X(t+\Delta_{X\to Y}),a_Y)}{\partial\varphi_X}\right)^2 d\varphi_X d\varphi_Y. \quad (4)$$

We used equations (5)–(7) proposed in Ref. [22] to determine the statistical significance of the evaluation of the coefficients $\gamma_X(\Delta_{Y\to X})=\overline{k_X^2}$ and $\gamma_Y(\Delta_{X\to Y})=\overline{k_Y^2}$:

$$\gamma_j=\overline{k_j^2}=\sum_k n_k^2 a_{j,k}^2-\sum_k n_k^2\sigma_{j,k}^2, \quad j=X,Y, \quad (5)$$

where

$$\sigma_{j,k}^2=\frac{2\sigma_{\varepsilon j}^2}{N}\left[1+2\sum_{i=1}^{\tau/\Delta t-1}(1-i\Delta t/\tau)\cos\Big((m_k a_{1,k}+n_k a_{2,k})i\Delta t/\tau\Big)\exp\Big(-(m_k^2\sigma_{\varepsilon 1}^2+n_k^2\sigma_{\varepsilon 2}^2)i\Delta t/2\tau\Big)\right].$$

The noise variance estimates $\sigma_{\varepsilon j}^2$ were calculated as follows:

$$\sigma_{\varepsilon j}^2=\frac{1}{N-1}\sum_{i=1}^{N}\left[\Big(\varphi_j(t_i+\tau)\Big)-\varphi_j(t_i)-\frac{1}{N}\sum_{i=1}^{N}\Big(\varphi_j(t_i+\tau)-\varphi_j(t_i)\Big)\right]. \quad (6)$$

The condition $\gamma_j(\Delta_{k\to j})-1.6\sigma_j(\Delta_{k\to j})>0$ was accepted as a criterion for the statistical significance of the influence $k\to j$, for which the estimates of the variance $\sigma_j(\Delta_{k\to j})$ of the values $\gamma_j(\Delta_{k\to j})$, $j=X, Y$, $k=Y, X$ were determined according to the formula

$$\sigma_j^2(\Delta_{k\to j})=\sum_k n_k^4\sigma_{j,k}^4. \quad (7)$$

This criterion corresponds to a 95% confidence interval. When the condition $\gamma_j(\Delta_{k\to j})-1.6\sigma_j(\Delta_{k\to j})>0$ is fulfilled, a conclusion is drawn about the statistical significance of the influence $k\to j$ with an error probability of no more than 0.05 [22].

The calculated estimates were used to plot curves for the dependence of the influence of the system Y on the system X on the delay time, $\gamma_X(\Delta_{Y\to X})$ and the dependence of the influence of the system X on the system Y on the delay time, $\gamma_Y(\Delta_{X\to Y})$ for multiple test delay times τ. The presence of a positive maximum on the graph of dependence $\gamma_X(\Delta_{Y\to X})$ indicates a delay of the effect of the system Y on the system X, and the location of

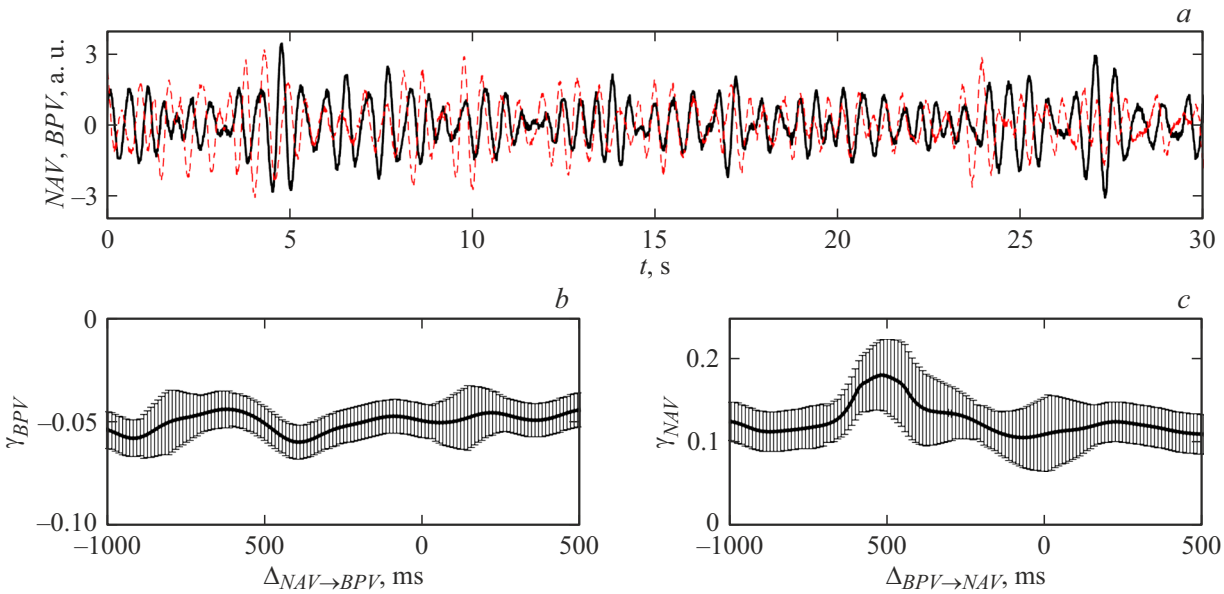

Figure 1. Estimation of delay times of the influence of the variability of neuronal activity intervals (NAV) on the variability of blood pressure intervals (BPV) and, conversely, the influence of variability of blood pressure intervals on variability of neuronal activity intervals: *a* — fragments of time series NAV (black solid curve) and BPV (red dashed dot curve); *b* — curve of the dependence of the influence $\gamma_{BPV}(\Delta_{NAV\to BPV})$ of variability of neuronal activity intervals (NAV) on variability of blood pressure intervals (BPV) on the delay time $\Delta_{NAV\to BPV}$ from the BPV side; *c* — curve of the dependence of the influence $\gamma_{NAV}(\Delta_{BPV\to NAV})$ of variability of blood pressure intervals (BPV) on variability of neuronal activity intervals (NAV) on delay time $\Delta_{BPV\to NAV}$ from the NAV side.

this maximum provides an estimate of the time delay $\Delta_{Y\to X}$ [7,23]. The presence of a positive maximum on the graph of dependence $\gamma_Y(\Delta_{X\to Y})$ indicates a delay of the effect of the system X on the system Y, and the location of this maximum provides an estimate of the time delay $\Delta_{X\to Y}$ [7,23].

2. Results

Fig. 1 shows an example of estimation of the delay time of the influence of the variability of neuronal activity intervals (NAV) on the variability of blood pressure intervals (BPV) and, conversely, the influence of BPV on NAV. 30-second fragments of the NAV and BPV time series are shown in Fig. 1, *a* by a black solid curve and a red dotted curve, respectively. These normalized time series are sequences obtained by narrowband filtering in the range from 1.5 to 2 Hz, i.e. near the frequency related to the characteristic period of blood pressure variability $T \sim 1/f_{BPV} = 0.53$ s for identifying a time delay of the linkage between these fluctuations in both time series.

The curve of the dependence of the effect $\gamma_{BPV}(\Delta_{NAV\to BPV})$ of NAV on BPV on the delay time $\Delta_{NAV\to BPV}$ from the BPV side (Fig. 1, *b*) is plotted with the variation of the test delay times. Similarly, Fig. 1, c shows the curve of the dependence of the effect $\gamma_{NAV}(\Delta_{BPV\to NAV})$ of BPV on NAV on the delay time $\Delta_{BPV\to NAV}$ from the NAV side. The test delay time varies from 0 to three characteristic periods of the analyzed BPV time series ($= 3T$, $T = 0.53\,\text{s} = 530\,\text{ms}$). Vertical lines on Fig. 1, *b* and *c* correspond to confidence intervals with 95% significance level.

The estimate of the influence of NAV on BPV on the dependence graph, along with the 95% confidence interval, has negative values (Fig. 1, *b*). This indicates that there is no statistical significance in this example in estimating the delay time of the influence of neuronal activity variability on blood pressure variability.

In contrast, the estimation of the BPV influence on NAV has positive values with a 95% confidence interval (Fig. 1, *c*). This indicates the statistical significance of the obtained estimate of the delay time of the influence of the BPV time series on the NAV time series with a 95% significance level. The magnitude of this delay is determined by the time interval corresponding to the maximum value of the dependence of the effect $\gamma_{NAV}(\Delta_{BPV\to NAV})$, and this value is 532 ms (Fig. 1, *c*).

An example of estimation of the delay time of the influence of respiratory rate fluctuations (RES) on BPV and, conversely, the influence of BPV on the respiratory rate is shown in Fig. 2. 30-second fragments of the RES and BPV time series are shown in Fig. 2, *a* with a black solid curve and a red dotted curve, respectively.

The analysis of the delay time of the influence of the analyzed RES time series on the BPV time series and, conversely, reveals the presence of positive maxima in the dependence $\gamma_{BPV}(\Delta_{RES\to BPV})$ (Fig. 2, *b*) and the absence of positive maxima in the dependence $\gamma_{RES}(\Delta_{BPV\to RES})$ (Fig. 2, *c*).

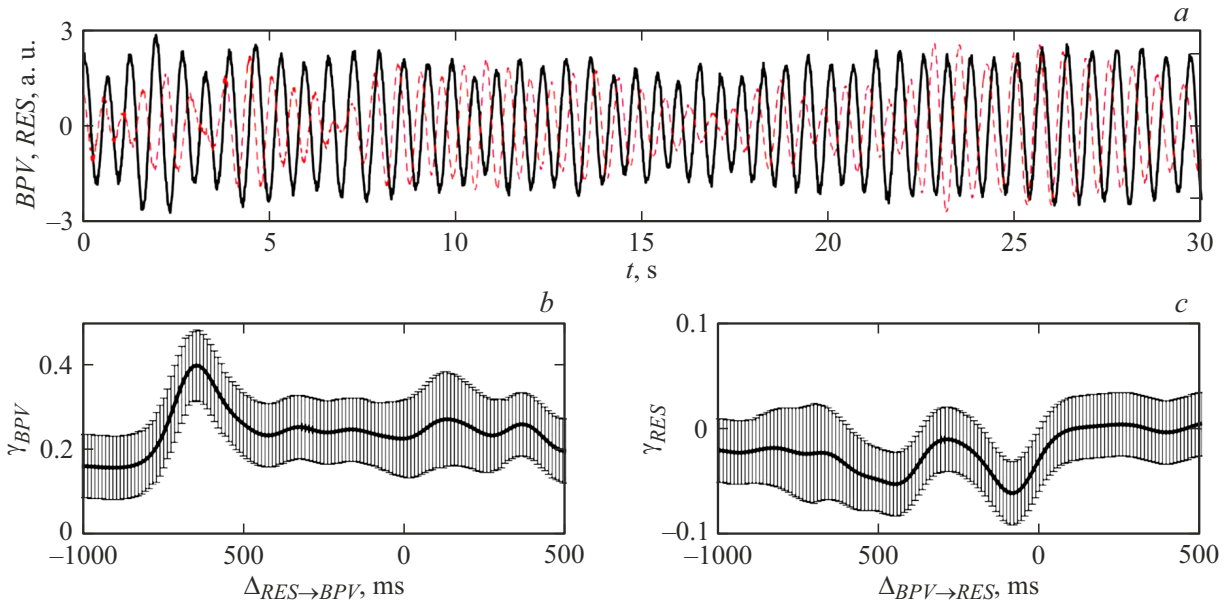

Figure 2. Estimation of the delay time of the influence of respiratory rate variability (RES) on blood pressure variability (BPV) and, conversely, the influence of blood pressure variability on respiratory rate *a* — fragments of the RES time series (black solid curve) and BPV (red dashed point curve); *b* — curve of the dependence of the influence$\gamma_{BPV}(\Delta_{RES\to BPV})$ of respiratory rate (RES) on blood pressure variability (BPV) on delay time $\Delta_{RES\to BPV}$ from the BPV side; *c* — curve of the dependence of the influence$\gamma_{RES}(\Delta_{BPV\to RES})$ of blood pressure variability (BPV) on the respiratory rate (RES) on delay time $\Delta_{BPV\to RES}$ from the RES side.

The values shown in the graph of dependence $\gamma_{BPV}(\Delta_{RES\to BPV})$ indicate the statistical significance of the obtained estimate of the delay time of the influence of the respiratory system on the cardiovascular system with a 95% significance level. The magnitude of this delay is 641 ms (Fig. 2, *b*), i.e. it is within the characteristic fluctuation period of the analyzed BPV time series of $T \sim 1/f_{BPV} = 662$ ms.

In contrast, the estimation of the influence of this BPV time series on the RES time series indicates that there is no statistical significance in estimation of the delay time of the influence of the cardiovascular system on the respiratory system in this example.

This study analyzed 17 unidirectionally linked BPV and RES time series with a prevalent influence of respiratory rate on blood pressure variability and 13 unidirectionally linked BPV and NAV time series with a prevalent influence of blood pressure variability on neuronal activity variability as defined in Ref. [17,19].

The table provides the data showing the number of time series for which the statistical significance of unidirectional influence $BPV \to NAV$ and $RES \to BPV$ was obtained with an error probability of no more than 0.05 before and during pain exposure. Unidirectional influence associated with positive values $\gamma_{NAV}(\Delta_{BPV\to NAV})$ and negative values $\gamma_{BPV}(\Delta_{NAV\to BPV})$ were found in 9 BPV and NAV time series before pain exposure and in 7 time series during pain exposure. The unidirectional influence associated with positive values $\gamma_{BPV}(\Delta_{RES\to BPV})$ and negative values $\gamma_{RES}(\Delta_{BPV\to RES})$ was found in 15 BPV and RES time series before pain exposure and in 12 time series during pain exposure.

Time series with obtained statistical significance of unidirectional influence $BPV \to NAV$ and $RES \to BPV$ and average time delays. The number of statistically significant values obtained with a 95% significance level was used for averaging

	Number of time series	
Unidirectional influence	Before pain exposure	During pain exposure
$\gamma_{BPV}(\Delta_{NAV\to BPV}) < 0$	9/13	7/13
$\gamma_{NAV}(\Delta_{BPV\to NAV}) > 0$	9/13	7/13
$\gamma_{BPV}(\Delta_{RES\to BPV}) > 0$	15/17	12/17
$\gamma_{RES}(\Delta_{BPV\to RES}) < 0$	15/17	12/17
Time delay		
$\Delta_{BPV\to NAV}$	571 ± 73 ms	595 ± 81 ms
$\Delta_{RES\to BPV}$	633 ± 92 ms	667 ± 99 ms

The average delay time of the influence of blood pressure variability on the neuronal activity variability, obtained by analyzing the dependence of the influence $\gamma_{NAV}(\Delta_{BPV\to NAV})$ on the delay time $\Delta_{BPV\to NAV}$, was 571 ± 73 ms before the pain exposure and 595 ± 81 ms during the pain exposure. The obtained delay times approximately correspond to one characteristic period of fluctuations of blood pressure variability, obtained using narrowband filtration near the respiratory rate frequency.

The average delay time of the influence of the respiratory rate on blood pressure variability was 633 ± 92 ms before the pain exposure and 667 ± 99 ms during the pain exposure.

Conclusion

The delay times in the interaction of time series extracted from biological rhythms associated with the nervous, respiratory, and cardiovascular systems in the form of variability of neuronal activity, blood pressure, and respiratory rate were determined based on modeling of phase dynamics and evaluation of statistical significance.

It was found that the average delay time of the influence of respiratory rate on blood pressure variability exceeds the delay time of the influence of blood pressure variability on the variability of neuronal activity intervals before and during pain exposure. Colorectal stretching results in an increase of the delay of the average delay times of both variants of influence.

An increase of the time of the delay of the influence of the respiratory system if its influence on the cardiovascular system is identified and the influence of the cardiovascular system on the nervous system during pain exposure may be associated with a complication of the mechanisms of functioning of interacting systems in case of colorectal stretching.

Compliance with ethical standards

All applicable international, national, and/or institutional guidelines for animal care and management were observed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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