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Citation: Chaos **28**, 081102 (2018); doi: 10.1063/1.5046758
View online: https://doi.org/10.1063/1.5046758
View Table of Contents: http://aip.scitation.org/toc/cha/28/8
Published by the American Institute of Physics

Synchronization of infra-slow oscillations of brain potentials with respiration

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(Received 1 July 2018; accepted 19 July 2018; published online 7 August 2018)

We study the synchronization of infra-slow oscillations in human scalp electroencephalogram signal with the respiratory signal. For the cases of paced respiration with a fixed frequency and linearly increasing frequency, we reveal the phase and frequency locking of infra-slow oscillations of brain potentials by respiration. It is shown that for different brain areas, the infra-slow oscillations and respiration can exhibit synchronous regimes of different orders. *Published by AIP Publishing.* https://doi.org/10.1063/1.5046758

The study of oscillatory cortical activity using scalp electroencephalogram (EEG) signals has a long history. However, the main attention in EEG signal analysis has been paid to the high-frequency rhythms. The neuronal mechanisms underlying the generation of brain low-frequency oscillations are still poorly understood. In the present paper, we focus on the study of such low-frequency rhythms representing infra-slow oscillations of brain potentials with a frequency of about 0.1 Hz. Investigations of infra-slow oscillations are promising for diagnostics of brain dysfunctions and for understanding the behavior processes. In spite of their importance, these oscillations of cortical activity are not well studied yet, especially in the awake state. We have examined for the first time the synchronization of infra-slow oscillations of brain potentials with respiration. It is found out that phase and frequency locking of infra-slow oscillations by respiration is typical under paced respiration. Moreover, for different brain areas, the infra-slow oscillations can exhibit different orders of synchronization with respiration. The obtained results contribute to a better understanding of the nature of infra-slow oscillations of brain potentials.

Steady potential variations of cerebral cortex representing the electroencephalogram (EEG) rhythms with a characteristic frequency less than 1 Hz have already been observed by Hans Berger in the first experiments on the recording of human EEG signals.[1] However, for a long period of time, the main attention in EEG signal analysis has been paid to the high-frequency rhythms: theta rhythm (4–8 Hz), alpha rhythm (8–12 Hz), beta rhythm (12–31 Hz), and others.[2] At the same time, many authors mentioned the importance of studying the steady potential variations; in particular, the infra-slow oscillations with a frequency of about 0.1 Hz and less.[3,4] Infra-slow oscillations are assigned to the delta-band[2] or classified as a separate band limiting the delta rhythm to the band 0.5–4 Hz.[5] Investigations of infra-slow oscillations contribute to the fundamental notion of the structure and dynamics of the autonomic nervous system.[3,6] Steady potential variations are studied for diagnostics of brain dysfunctions and diseases,[7–12] for understanding the behavior processes,[5,13–15] and for the scoring of sleep.[16]

Some authors reported that steady potential variations and delta-band oscillations are the reflection of the autonomic nervous system activity rather than a direct consequence of cerebral cortex activity.[3,4] It has been revealed that steady potential variations are associated with the regulation of the heart rate, arterial pressure, respiration, and other processes.[17,18] The origin of steady potential variations is associated with regulatory activities at different levels of the central and autonomic nervous system.[3,5,6,17] Knyazev stated that steady potential variations must participate in synchronization of brain activity with autonomic functions.[5]

In spite of their importance, the steady potential variations and infra-slow oscillations, in particular, are not well studied yet.[11] For example, there are practically no studies of steady potential variations in the awake state, since the activation of various brain areas in this case impedes the linear correlation analysis and spectral analysis of EEG low-frequency components having, as a rule, small amplitudes.[5] The promising results have been obtained in Ref. 6 by applying various nonlinear methods to the analysis of multichannel data of anesthetized dogs. In particular, Vandenhouten *et al.* detected phase synchronization between systolic blood pressure, efferent renal sympathetic nerve activity, and brainstem neurons whose signals were recorded extracellularly.[6] Moreover, the interaction has been revealed between the infra-slow oscillations in the signals of occipital EEG leads and extracellularly recorded neurons of reticular formation of the common brainstem system.[6,18] However, the limitations of these studies were the employment of only the methods of passive observation and the absence of statistical analysis of the obtained results.

Our study is aimed at examination of interaction between the respiration and infra-slow oscillations in EEG signals in healthy humans during experiments with controlled frequency of breathing. The study of the interaction of respiration with various physiological processes including brain neuronal activity is important and promising for understanding the functioning and interaction of various human systems in health and disease.[19] In this paper, we report for the first time the presence of synchronization of infra-slow oscillations of human brain potentials with respiration. This result contributes to a better understanding of the nature of infra-slow oscillations.

We studied 13 subjects aged 22–32 years whose non-invasive scalp EEG and respiratory signals were simultaneously recorded in a supine resting condition with closed eyes. All the subjects signed a written consent. The experimental studies were performed in accordance with the Declaration of Helsinki and approved by the local research Ethics Committee of the Yuri Gagarin State Technical University of Saratov. International 10–20 system was used for placement of 19 EEG electrodes. All signals were recorded with a sampling frequency of 2 kHz and 24-bit resolution. Three experiments were carried out with each subject under different regimes of breathing.

First, the signals were registered during paced respiration whose frequency was linearly increasing from 0.05 Hz to 0.25 Hz within 30 min. The rate of breathing was set by short sound pulses. To extract the infra-slow oscillations of brain potentials from EEG, we filter the EEG signal removing the oscillations with the frequencies below 0.05 Hz and above 0.25 Hz. In the second experiment, the time intervals of spontaneous breathing alternated with the intervals of fixed-frequency breathing, in which the rate of breathing was set by sound pulses. In the intervals of fixed-frequency breathing, each lasting 400 s, the frequency of respiration was fixed at 0.08 Hz, 0.12 Hz, and 0.21 Hz in the first, second, and third intervals, respectively. The total duration of the second experimental session was 1960 s (about 33 min). For extracting the infra-slow oscillations in this case, we use the bandpass filtration of the EEG signal with a bandpass of 0.05–0.3 Hz. The third experiment lasting 25 min was carried out with each subject under spontaneous breathing.

We apply different methods for the analysis of phase and frequency locking between the infra-slow oscillations and respiratory signal. At first, we calculate the instantaneous phases $\phi_p(t)$ of infra-slow oscillations and $\phi_r(t)$ of respiration using the Hilbert transform.[20] Then, we define the phase difference

$$\varphi_{n,m}(t) = n\phi_p(t) - m\phi_r(t), \tag{1}$$

where n and m are integers and calculate the phase synchronization index

$$\gamma_{n,m} = |\langle \exp[i\varphi_{n,m}(t)]\rangle_t| = \sqrt{\langle \cos\varphi_{n,m}(t)\rangle_t^2 + \langle \sin\varphi_{n,m}(t)\rangle_t^2}, \tag{2}$$

where angular brackets denote average over time.[21] By construction, $\gamma_{n,m} = 0$ if the oscillations are not synchronized at all and $\gamma_{n,m} = 1$ in the case of perfect synchronization.

Figure 1(a) shows the time evolution of $\gamma_{1,1}$ for subject A under linearly increasing frequency of respiration. Each point in Fig. 1(a) is calculated for a window of 100 s. To avoid

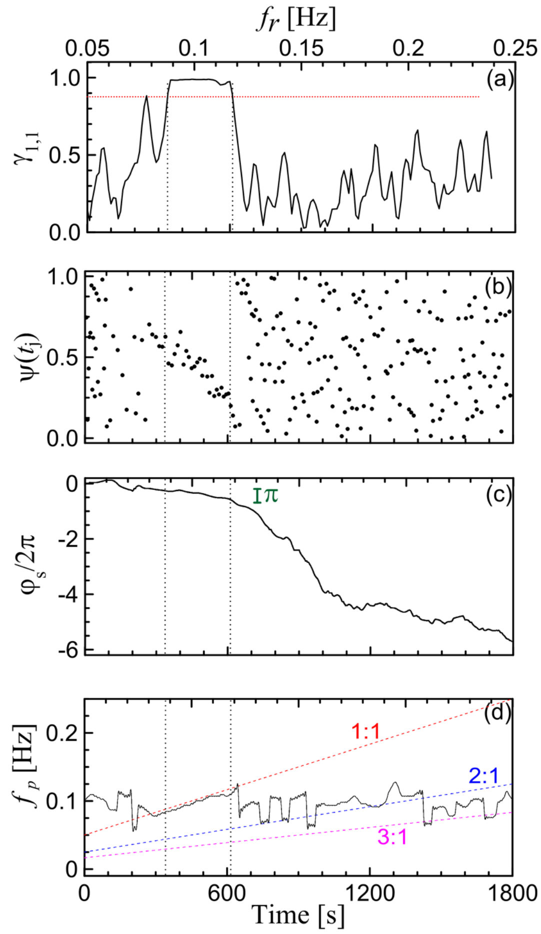

FIG. 1. Measures of synchronization of infra-slow oscillations (EEG electrode placement at O1) by the respiratory signal with linearly increasing frequency for subject A. (a) Phase synchronization index. Dashed line shows a significance level of $p = 0.05$. (b) Synchrogram. (c) Phase difference between the signal of infra-slow oscillations and the signal of respiration. (d) Dependence of the frequency of infra-slow oscillations on the respiratory frequency. Dashed lines are the lines along which f_r is a multiple of f_p.

spurious detection of phase locking, we derive significance level p by applying the same analysis to surrogate data. The phase synchronization index $\gamma_{1,1}$ is close to unity within the interval 340–610 s (0.088–0.118 Hz), indicating the presence of 1:1 phase synchronization. This region is bounded in Fig. 1 by the vertical dotted lines.

The presence of synchronization between the analyzed signals is also demonstrated in our study by plotting a synchrogram.[22] To construct a synchrogram [Fig. 1(b)], we determine the phase ϕ_p at time moments t_j when the cyclic phase of the respiratory signal attains a certain fixed value θ, $\phi_r(t_j) \bmod 2\pi = \theta$, and plot $\psi(t_j)$ versus t_j, where

$$\psi(t_j) = \frac{1}{2\pi}[\phi_p(t_j) \bmod 2\pi]. \tag{3}$$

In the case of n:1 synchronization, the synchrogram exhibits n lines.[22] At the respiratory frequencies 0.095–0.12 Hz, the synchrogram in Fig. 1(b) has nearly one-band structure showing some indication of 1:1 synchronization between the infra-slow oscillations and respiration.

As a second approach for calculating the instantaneous phases and frequencies of the studied signals, we use the continuous wavelet transform[23,24]

$$W(s,t_0) = \frac{1}{\sqrt{s}} \int_{-\infty}^{+\infty} x(t)\Psi^*_{s,t_0}\left(\frac{t-t_0}{s}\right) dt \qquad (4)$$

of the signal $x(t)$, where Ψ is the mother-wavelet function, s is the time scale, t_0 is the time shift, and the asterisk denotes complex conjugation. As the mother-wavelet function, we use the Morlet wavelet.[25] The wavelet spectrum

$$W(s,t_0) = |W(s,t_0)| \exp[i\phi_s(t_0)] \qquad (5)$$

describes the system dynamics for every time scale s at any time moment t_0. The value of $|W(s,t_0)|$ determines the intensity of the time scale s at the moment of time t_0. At the same time, the phase $\phi_s(t) = \arg W(s,t)$ is naturally defined for every time scale s associated with the frequency f of the signal $x(t)$.[26]

In the case of the respiratory frequency increasing in accordance with *a priori* known linear law: $f_r(t) = a + bt/T$, where $a = 0.05$ Hz, $b = 0.20$ Hz, and $T = 1800$ s, we calculate the instantaneous phase $\phi_{sp}(t)$ of infra-slow oscillations in the EEG signal along the scale $s_r(t) = 1/f_r(t)$, corresponding to the varying frequency of respiration. The phase difference $\varphi_s(t) = \phi_{sp}(t) - \phi_{sr}(t)$, where $\phi_{sr}(t) = 2\pi[(a + bt/2T)]t$ is the phase of respiration, is plotted in Fig. 1(c). Between 400 s and 600 s, $\phi_s(t)$ decreases by π. Such behavior of $\phi_s(t)$ agrees well with the theoretically derived variation of the phase difference in the region of synchronization of oscillator by external driving with linearly varying frequency.[27]

To detect the locking of the basic frequency f_p of infra-slow oscillations by the linearly increasing frequency f_r of respiration, we plot the dependence of f_p on f_r [Fig. 1(d)]. The frequency f_p is calculated using the continuous wavelet transform. The presence of 1:1 frequency locking is clearly seen under respiratory frequencies 0.085–0.12 Hz [Fig. 1(d)]. We observe also the regions where the instantaneous frequency ratio f_r/f_p is close to 2:1 and 3:1. The dependence $f_p(f_r)$ depicted in Fig. 1(d) repeats the classical picture of oscillator frequency locking by external forcing with varying frequency.[28]

We analyze the duration of epochs of 1:1 synchronization between the respiration and infra-slow oscillations of brain potentials using the signals from all EEG electrodes for each subject (Fig. 2). We reveal that the longest intervals of synchronization between the considered processes are observed in the occipital area in the left hemisphere of brain. In the other brain areas, the synchronization of infra-slow oscillations and respiration is either worse or not observed at all. The longest epoch of synchronization is observed for subject B in the case of electrode placement at O1. The duration of this epoch of synchronization is 624 s. The duration of synchronization epochs averaged over all EEG electrodes and all subjects is 177 ± 127 s (mean ± standard deviation).

Figure 3 shows the results of synchronization analysis for the case, where the time intervals of spontaneous breathing alternated with the intervals of fixed-frequency breathing. The phase synchronization indices $\gamma_{1,1}$ and $\gamma_{2,1}$ for subject

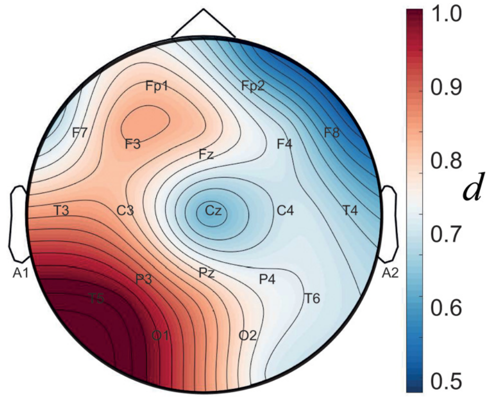

FIG. 2. Duration d of epochs of 1:1 synchronization between the respiration with linearly increasing frequency and infra-slow oscillations in different brain areas. For each placement of the EEG electrode, the values of d are averaged over all subjects and normalized to the maximal d value over all electrodes.

A for the case of EEG electrode placement at T5 are presented in Fig. 3(a). The values of $\gamma_{1,1}$ and $\gamma_{2,1}$ are close to unity in the regions of respiration with the fixed frequencies of 0.08 Hz and 0.21 Hz, respectively, indicating the presence of 1:1 and 2:1 phase synchronization between the respiration and infra-slow oscillations. The synchrogram also gives some indication of the presence of synchronization in the intervals of fixed-frequency breathing [Fig. 3(b)].

In the case of EEG electrode placement at O1, P3, and Pz, we obtain qualitatively similar results. These results suggest that the projections of activity of different brain structures on EEG electrodes are associated with several self-oscillating processes having close frequencies, which are affected by the signal of respiration. The observation of different orders of synchronization of infra-slow oscillations in different brain areas also counts in favor of such an assumption.

Figure 4 shows the orders of synchronization detected between the respiration with a fixed frequency and infra-slow oscillations for different placements of EEG electrodes for subject A. For the majority of electrodes, we observe

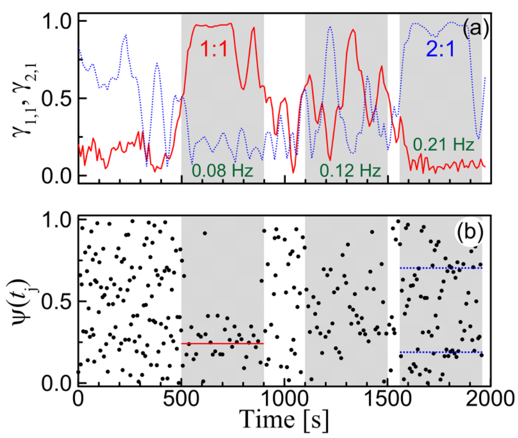

FIG. 3. Phase synchronization indices $\gamma_{1,1}$ (solid line) and $\gamma_{2,1}$ (dotted line) (a) and synchrogram (b) for subject A for the case of EEG electrode placement at T5. The time intervals of spontaneous breathing are shown in white color. The time intervals of breathing with a fixed frequency equal to 0.08 Hz, 0.12 Hz, and 0.21 Hz are shown in gray color.

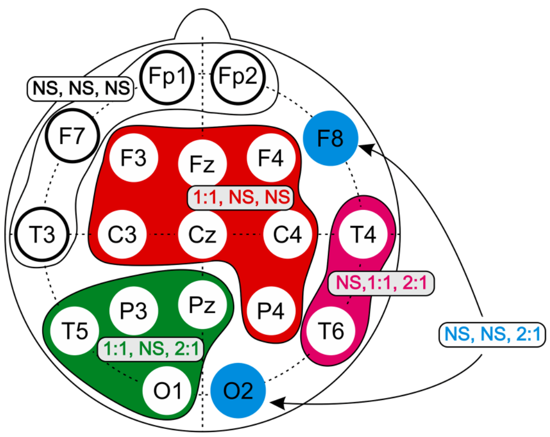

FIG. 4. Scheme of synchronization of infra-slow oscillations of brain potentials by the respiratory signal with a fixed frequency equal to 0.08 Hz, 0.12 Hz, and 0.21 Hz for subject A. The electrodes for which the infra-slow oscillations exhibit similar synchronous and nonsynchronous regimes at each of the three fixed frequencies of respiration are depicted in the same color. The absence of synchronization is denoted as NS.

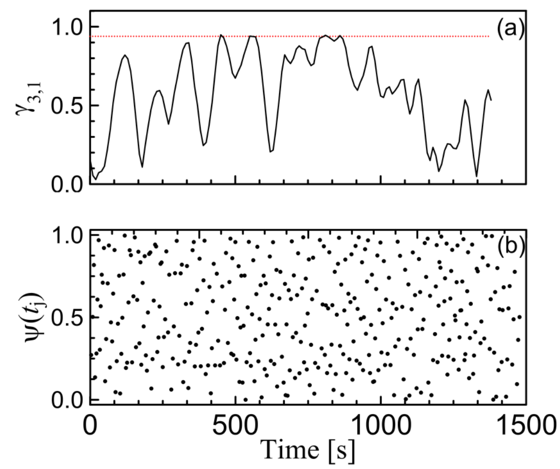

FIG. 5. Phase synchronization index $\gamma_{3,1}$ (a) and synchrogram (b) for subject C under spontaneous breathing for the case of EEG electrode placement at O1. Dashed line in (a) shows a significance level of $p = 0.05$.

1:1 synchronization between the considered rhythms. For six electrodes, we detect 2:1 synchronization at one frequency of respiration and 1:1 synchronization at another frequency of respiration.

It is interesting to note that in the case of spontaneous breathing, we find no evident indications of the presence of any kind of synchronization between the infra-slow oscillations and respiration. The phase synchronization index $\gamma_{3,1}$ is presented in Fig. 5(a) for subject C under spontaneous breathing for the case of EEG electrode placement at O1. For short intervals of time, this index takes sufficiently high values, but these values are not significant. Since the average frequency of spontaneous breathing for subject C is about 0.28 Hz, we plot in Fig. 5(a) only the index $\gamma_{3,1}$. The other phase synchronization indices take much lower values. The similar picture is observed for other placements of electrodes and other subjects. The synchrogram does not exhibit any n-band structure [Fig. 5(b)]. Thus, the paced respiration with a certain frequency is a critical condition for the presence of synchronization between the infra-slow oscillations and respiration.

For the case of spontaneous breathing, we calculate the coherence function between the infra-slow oscillations and respiration:

$$C_{pr}(f) = \frac{|G_{pr}(f)|}{\sqrt{G_{pp}(f)G_{rr}(f)}}, \tag{6}$$

where $G_{pp}(f)$ and $G_{rr}(f)$ are the power spectra of the signals of infra-slow oscillations and respiration, respectively, and $G_{pr}(f)$ is a cross spectrum:

$$G_{pr}(f) = \langle F_p(f)F_r^*(f)\rangle, \tag{7}$$

where $F_p(f)$ is the Fourier transform of infra-slow oscillations in the EEG signal, $F_r(f)$ is the Fourier transform of the respiratory signal, the asterisk denotes complex conjugation, and angular brackets denote average over time.[21,29] The coherence function takes the values between zero and unity and characterizes the phase coherence between oscillations for the frequency f. It can be considered as a linear measure of synchronization.

The coherence between the infra-slow oscillations and respiration takes the maximal values at the frequencies close to the frequency of respiration. However, these values are low for most of the brain areas. Figure 6 depicts the maximal values of coherence function (6) averaged over all subjects. The highest values of coherence function are observed in the occipital area in the left hemisphere of brain. In this area, the coherence is about 0.6. Note that the same area of brain exhibits the best synchronization of infra-slow oscillations by respiration with linearly increasing frequency (see Fig. 2).

Thus, in the case of spontaneous breathing of subjects, we failed to reveal the synchronization of infra-slow oscillations of brain potentials with respiration. In contrast to the case, in which one cannot interfere in the experiment, an active experiment, in which it is possible to control the parameters of external forcing, is one of the most promising methods for revealing interactions between complex systems.[30]

The experiments under subjects' paced respiration allow us to detect strong interaction between the respiration and

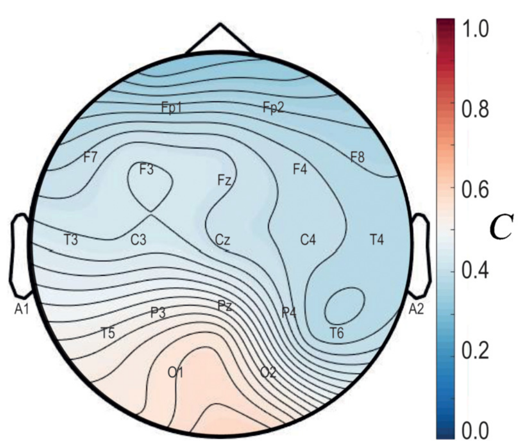

FIG. 6. Maximal values of the coherence function between the infra-slow oscillations and respiration averaged over all subjects under spontaneous breathing.

infra-slow oscillations in scalp EEG. This interaction results in phase and frequency locking of the considered brain rhythms by respiration. This is evidenced by the fact of observation of the change of π in the phase difference in the active experiments with the breathing with a variable frequency.[27] However, due to non-stationarity and complexity of signals of living systems, synchronization can sometimes alternate with intermediate regimes, the analysis of which is a complex task and requires further consideration. It is shown for the first time that for different brain areas, the infra-slow oscillations can exhibit different orders of synchronization with respiration. We suppose that in the brain structures there are several self-oscillating processes (the so-called central pattern generators) with the basic frequency close to 0.1 Hz, which are responsible for the generation of infra-slow oscillations of brain potentials. Most likely these infra-slow rhythms of cortical activity are associated with the rhythms of autonomic control of the heart rate and blood pressure, which have basic frequencies of about 0.1 Hz[31] and show similar synchronization with respiration.[32] The obtained results contribute to a better understanding of the origin of infra-slow oscillations of brain potentials. In further research, we plan to compare the features of synchronization between the respiration and infra-slow oscillations in EEG in healthy subjects and patients and to study the possibility of using the obtained results for medical diagnostics.

ACKNOWLEDGMENTS

This work was supported by the Ministry of Education and Science of Russian Federation (Agreement No. 3.861.2017/4.6) in the part of an experimental study and processing of experimental data and Russian Science Foundation (Grant No. 14-12-00224) in the part of development of mathematical methods of EEG signals processing. A.E.H. acknowledges individual support from the Ministry of Education and Science (Russia) (Agreement No. 3.4593.2017/6.7) for the development of the experiment design.

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