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# Biomarkers of the psychophysiological state during the cognitive tasks estimated from the signals of the brain, cardiovascular and respiratory systems

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**Abstract** Diagnostics of the psychophysiological state at rest and under stressful conditions is an important problem. We tested various biomarkers of the psychophysiological state of healthy volunteers at rest and while completing stress-inducing cognitive tasks, namely the Stroop color word test and mental arithmetic test. We tested the biomarkers based on the analysis of electroencephalograms, respiratory signals, and the signals of cardiovascular system. We investigated both the individual characteristics of these signals in the low-frequency range (less than 0.5 Hz), and characteristics of their interaction. According to our results, the most sensitive biomarkers of cognitive task stress are nonlinear phase coherence between the 0.15 and 0.40 Hz oscillations in the respiratory signal and heart rate variability, and integral power of the 0.15–0.40 Hz oscillations in the frontal lobe EEG leads.

## 1 Introduction

Quantitative estimation estimation of the psychophysiological state and its relation to the performance of the cognitive tasks is an important and complex problem [1, 2]. Stress affects health, speed of decision making and employee efficiency. Apart from the medical diagnostics, investigation and quantification of the effects of stress is also important for the development of neurointerfaces.

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Currently, questionnaire surveys are accepted as the reference method for estimation of the psychophysiological state [3–5]. However, this approach is subjective, and it is unclear how to extract quantitative indices from its results [2]. Another perspective approach is the analysis of biological signals and investigation of their individual characteristics and characteristics of interaction between these signals [1, 2]. The commonly used signals are arterial pressure (AP) [6–8], electrodermatogram (EDG) [9–11], electroencephalogram (EEG) [1, 2, 12], electromyogram (EMG) [13–15], skin temperature [16–18], pupil dilatation [19–21], cortisol level [22, 23], and saliva α-amylase level [24]. The methods using near-infrared spectrometry (fNIRS) [25], positron emission tomography (PET) [26], and functional magnetic resonance imaging (fMRI) [27] are also widely employed. The analysis of respiratory signals [18, 28, 29], photoplethysmograms (PPG) [30–34], and RR-intervals (the intervals between the well-pronounced R peaks in an electrocardiogram (ECG)) [35–39], is promising for the development of ergonomic lightweight wearable devices for stress detection.

The analysis of EEG signals is commonly carried out in the time-domain [2] or in the frequency-domain

[1]. The most commonly used frequency ranges are the delta range (0.5–4 Hz) [40–42], theta range (4–8 Hz) [40–43], alpha range (8–13 Hz) [40–42, 44], beta range (13–30 Hz) [12], and gamma range (30–50 Hz) [43], which are related to the different physiological processes [2]. According to the review [1], correlation between the symmetric EEG leads in the alpha, beta, and theta ranges changes under stress [45–49] and is, therefore, promising for its diagnostics.

The problem of the psychophysiological state diagnostics was studied by many authors. However, the results are often contradictory, as was concluded in [1, 2]. Among the likely reasons for this are the lack of accepted standards for measuring and interpreting results, as well as the nonstationarity of the behavior of biological signals [50]. Oscillations in the delta, theta, alpha, beta, and gamma ranges reflect the activity of the cortical neurons. The neurons are affected by many physiological and psychological factors, which are hard to control and standardize. The analysis of low-frequency oscillations associated with the activity of autonomic control of circulation that respond to changes in the psychophysical state of a person, may turn out to be more promising. The activity of the autonomic control is reflected in the heart rate variability, which is often estimated from the sequence of RR-intervals (RRi) [51]. Low-frequency oscillations (LF, 0.04–0.15 Hz) in the RRi are mainly associated with the effects of the sympathetic branch of the autonomic control on the heart rate. The high-frequency oscillations (HF, 0.15–0.4 Hz) are mainly associated with the effects of the parasympathetic control [51]. The frequency of the main peak in the HF band corresponds to the frequency of the respiration [51]. In [52–55], the infra-slow oscillations of brain potentials in EEG (0–0.5 Hz) were mainly associated with the activity of the autonomic control of circulation. Therefore, one can expect that these infra-slow oscillations are more stationary comparing to oscillations in high-frequency ranges of EEG.

Thus, there is physiologically based evidence that the properties of the infra-slow oscillatory activity of the EEG, along with the respiratory signal and oscillations in the LF and HF ranges in RRi can be used as biomarkers of the psychophysiological state and, in particular, stress. In this study, we aimed to test the individual characteristics of these signals and characteristics of their interaction.

## 2 Design of the study and the experimental data

We studied 30 healthy subjects aged 21 ± 3 years (mean ± standard deviation), having average levels of physical activity. Cognitive testing consisted of Stroop color word test (SCWT) [56] and mental arithmetic test (MT) [57], which are considered standard procedure for inducing moderate level of stress [2].

The study protocol was as follows: 6-min resting period (R0), 6 min of SCWT (S1), 6-min resting period (R1), 6 min of MT (S2), 6-min resting period (R2) (Fig. 1a). During the R0, R1, and R2 stages, the volunteer was instructed to remain sitting in a comfortable chair and relax. During the SCWT, the volunteer was presented with a sequence of colored words—names of a color, for which the color of the letters mismatched with the color referred by the word. Overall, 360 combinations, presented in random order at 1-s intervals. The volunteer was instructed to deduce and internally pronounce the color of the letters (Fig. 1b). During the MT, the volunteer was presented with three- and four-digit numbers, changing each 5 s. The volunteer was instructed to sum the digits before they change. If the resulted number contained two digits, they should be summed again, continuing this cycle until the resulting number is a single digit. After calculating the single-digit number, the volunteer was instructed to decide whether the number is even or odd and press the corresponding button (Fig. 1c). Overall, each volunteer was presented with a set of 72 numbers.

During the testing, we recorded the signals of ECG, EEG using 8–3 system for electrode placement, PPG from the distal phalanx of the left ring finger ($PPG_f$), and PPG from the right earlobe ($PPG_e$). All signals were recorded using the standard certified digital electrocardiograph Encefalan_EEGP-19/26 [58] with 250 Hz sampling frequency. Band pass filter was set to 0.5–70 Hz for ECG; 0.05–30 Hz for $PPG_f$ and $PPG_e$, 0–40 for respiration, and 0.016–70 Hz for EEG.

## 3 Data analysis

The RRi were extracted from ECG according to the recommendations [51]. Then the RRi were linearly interpolated and resampled with a frequency of 5 Hz. The power spectra were estimated for each experimental signal (RRi, $PPF_f$, $PPG_e$, 8 EEG leads, and respiration). The spectral analysis was also performed according to the recommendations [51]. Then we analyzed the LF and HF oscillations [51] separately for each stage: R0, S1, R1, S2, and R2.

For the raw nonequidistant RRi, we calculated the mean value of heart rate (HR), standard deviation (SDRR), and the root-mean-square of successive differences between heartbeats (RMSSD). For the resampled RRi, we calculated the normalized power in the LF-range (nLF-RRi), the normalized power in the HF-range (nHF-RRi), and the LF/HF ratio (LF/HF-RRi). For each EEG signal, we estimated the normalized power in the LF-range (nLF-EEG), the normalized power in the HF-range (nHF-EEG), and the LF/HF ratio (LF/HF-EEG). For the F3–F4 pair of EEG leads, we calculated the alpha-band power asymmetry index (APA-EEG) [59].

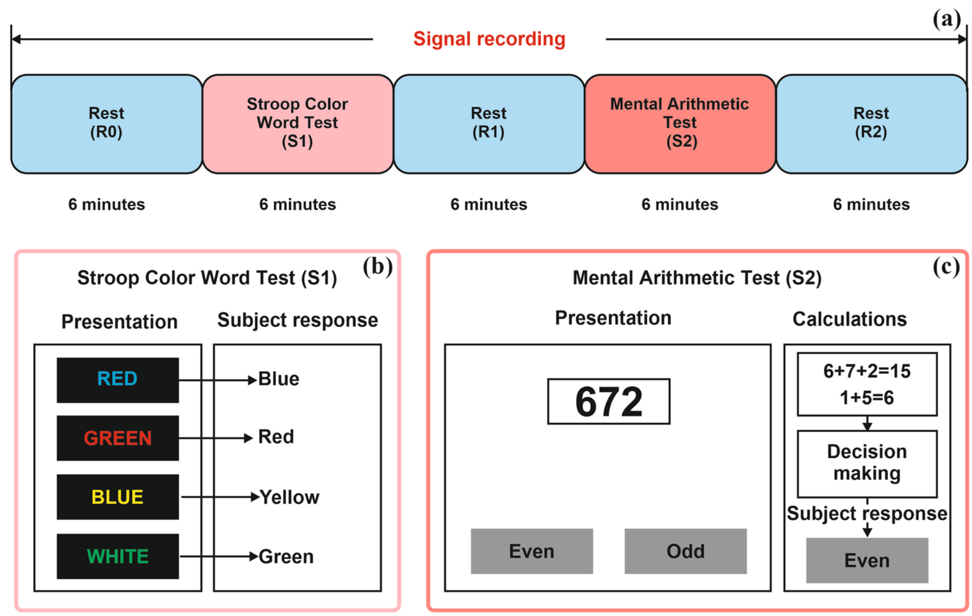


**Fig. 1** **a** Protocol of the stress test. **b** Stroop color word test. **c** Mental arithmetic test

To estimate the measure of interaction between the systems, which generate the LF and HF oscillations in the EEG, RRi, $PPG_f$, $PPG_e$ and respiration we calculated the specific phase coherence (SPC) proposed in [60]. SPC was calculated between the HF-oscillations in RRi and respiration ($SPC_{HF}$(RRi, Br)), LF-oscillations in RRi and $PPG_f$ ($SPC_{LF}$(RRi, $PPG_f$)), LF-oscillations in RRi and $PPG_e$ ($SPC_{LF}$(RRi, $PPG_e$)), LF-oscillations in the symmetrical EEG leads $SPC_{LF}$(EEG, sEEG), HF-oscillations in the symmetrical EEG leads $SPC_{HF}$(EEG, sEEG), LF-oscillations in RRi and EEG leads $SPC_{LF}$(RRi, EEG), HF-oscillations in RRi and EEG leads ($SPC_{HF}$(RRi, EEG)), and HF-oscillation in EEG and respiration ($SPC_{HF}$(EEG, Br)).

Individual values of the indices obtained for each stage of the experiment were averaged over the ensemble. The statistical significance of the difference between the stages was controlled using the Mann–Whitney $U$-test with $p < 0.05$ [61]. Also, we calculated the differences in each index between the stages R0-S1 and R1-S2 for each volunteer. The differences were also averaged.

The receiver operating characteristic curves (ROC-curves) and the arias under the ROC-curves (AUC) were used to determine the threshold values of the indices that provide the best sensitivity and specificity when classifying the states of volunteers (stages R1 and S2) and relaxed volunteers (stages R0 and S1).

## 4 Results

Figure 2 compares the values of indices most commonly used for stress diagnostics calculated for stages R0, S1, R1, S2, and R2. Figure 2 shows that cognitive task increases the group-averaged heart rate (Fig. 2a) and decreases both the RMSSD (Fig. 2b) and SDRR (Fig. 2c). We also observed changes in the asymmetry index for the power of the alpha-band oscillations in the F3 and F4 EEG leads, namely increased power of the alpha-band oscillations in the right hemisphere in relation to the left hemisphere (Fig. 2d). It agrees well with the results of other well-known studies [2]. However, the Mann–Whitney U-test did not confirm the statistical significance of the differences between the stages of performing cognitive task and resting stages, which can be explained by relatively small changes in mean values of HR (Fig. 2a), RMSSD (Fig. 2b), and SDRR (Fig. 2c) and large variance of the APA-EEG index (Fig. 2d).

Figure 3 shows the results of the spectral analysis of the LF-oscillations. The spectral indices estimated from the $PPG_e$ exhibit changes during the SCWT and MT tests. The power of the LF-oscillations increases (Fig. 3a), the power of the HF-oscillations decreases (Fig. 3b), and, as a result, the LF/HF-$PPG_e$ also increases (Fig. 3c). The spectral indices estimated from the $PPG_f$ and RRi signals have less pronounced reaction to the mental task (Fig. 3d–i). The power of both LF- and HF-oscillations in the $PPG_f$ signal increases during the SCWT and MT tests (Fig. 3d, e) and the LF/HF-$PPG_f$ index (Fig. 3 f) also increases. In the RRi signal, the power of the LF-oscillations only increases at the S2 stage, in relation to the R1 stage (Fig. 3g); the power of the HF-oscillations only decreases at the S1 stage, in relation to the R0 stage (Fig. 3h), and, as a result, the LF/HF-RRi index only increases at the S1 stage in relation to the R0 stage (Fig. 3i). Although Fig. 3 shows noticeable changes in the mean values of the aforementioned spectral indices between the stages of rest and cognitive task, they were not statistically significant.

In contrast, the spectral indices estimated from the EEG signals show statistically significant changes during the cognitive test. The mean value of the nHF-EEG significantly decreases at the S1 and S2 stages. When averaging the changes of the nHF-EEG index between

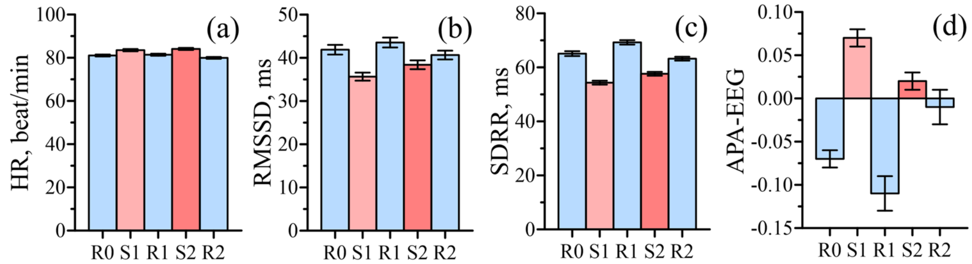


**Fig. 2** Mean values and their standard error for the following indices: (**a**) HR, (**b**) RMSSD, (**c**) SDRR, and (**d**) APA-EEG

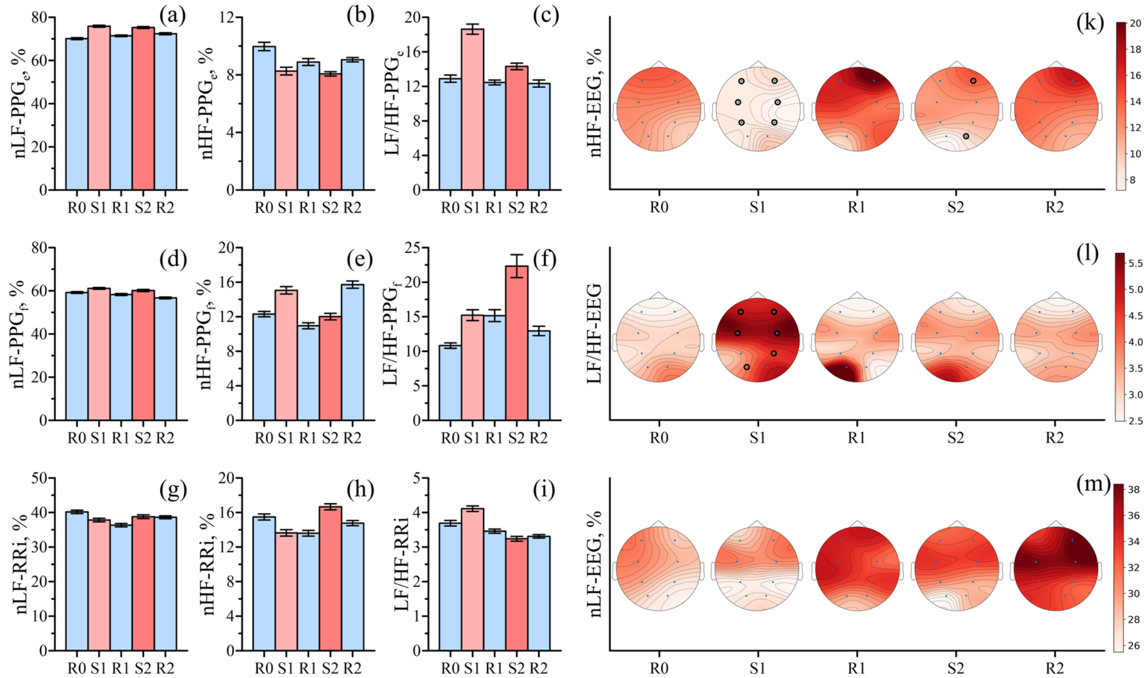


**Fig. 3** Mean values and their standard error for the following spectral indices: (**a**) nLF-PPG$_e$, (**b**) nHF-PPG$_e$, (**c**) LF/HF-PPG$_e$, (**d**) nLF-PPG$_f$, (**e**) nHF-PPG$_f$, (**f**) LF/HF-PPG$_f$, (**g**) nLF-RRi, (**h**) nHF-RRi, and (**i**) LF/HF-RRi. Color-coded maps of the mean values of the EEG leads for the following spectral indices: (**k**) nHF-EEG, (**l**) LF/HF-EEG, and (**m**) nLF-EEG. The black circles mark the EEG leads, for which the mean value of the spectral indices at the stages S1 and S2 are significantly different from the stages R1 and R2 (according to the Mann–Whitney $U$-test at $p < 0.05$)

the S1 and R0 stages over all leads showing the significant changes, we obtain the index decrease by 3.8 $\pm$ 0.2%. This effect was observed for all leads, except for the occipital leads (Fig. 3k). Between the S2 and R1 stages, the average decrease in power is 3.2 $\pm$ 0.3% (mean $\pm$ standard error), and the statistically significant changes were detected for the F4 and O2 leads (Fig. 3k). The LF/HF-EEG index for the P4 and O1 leads is significantly larger at the S1 stage comparing to the R0 stage (Fig. 31) and shows no significant changes between the S2 and R1 stages (Fig. 3l). At average, the LF/HF-EEG index at the S1 stage is 1.7 $\pm$ 0.1% larger in comparison to the R0 stage (Fig. 3l). Such dynamics can be mostly attributed to the changes in the power of the HF-oscillations, since the values of the nLF-EEG (рис. 3 m) index at the stages S1 and S2 are not significantly different from its values at the stages R1 and R2.

Figure 4 shows the results of the phase coherence analysis. The $SPC_{HF}$(RRi, Br) index associated with the cardiorespiratory coupling shows the most noticeable reaction to the cognitive task (Fig. 4a). It decreases by 0.17 $\pm$ 0.01 (mean $\pm$ standard error) between the stages R0 and S1, and decreases by 0.21 $\pm$ 0.01 between the stages R1 and S2 (Fig. 4a). The changes are statistically significant and agree with the results [28, 62], which state that stress suppresses the respiratory sinus arrhythmia.

The phase coherence between the LF-oscillations in the RRi and PPG, conversely, slightly increases under the cognitive task (Fig. 4b,c). However, the changes are not statistically significant. This can be explained by the results from [2], where the authors notice the activation of the autonomic nervous system under stressful conditions.

Figures 4d–h show the values of SPC in different brain areas for several pairs of signals. The darker color corresponds to higher values of the SPC. Panels (d) and (e) show the coherence between the symmetrical EEG leads in the LF and HF ranges, respectively. We

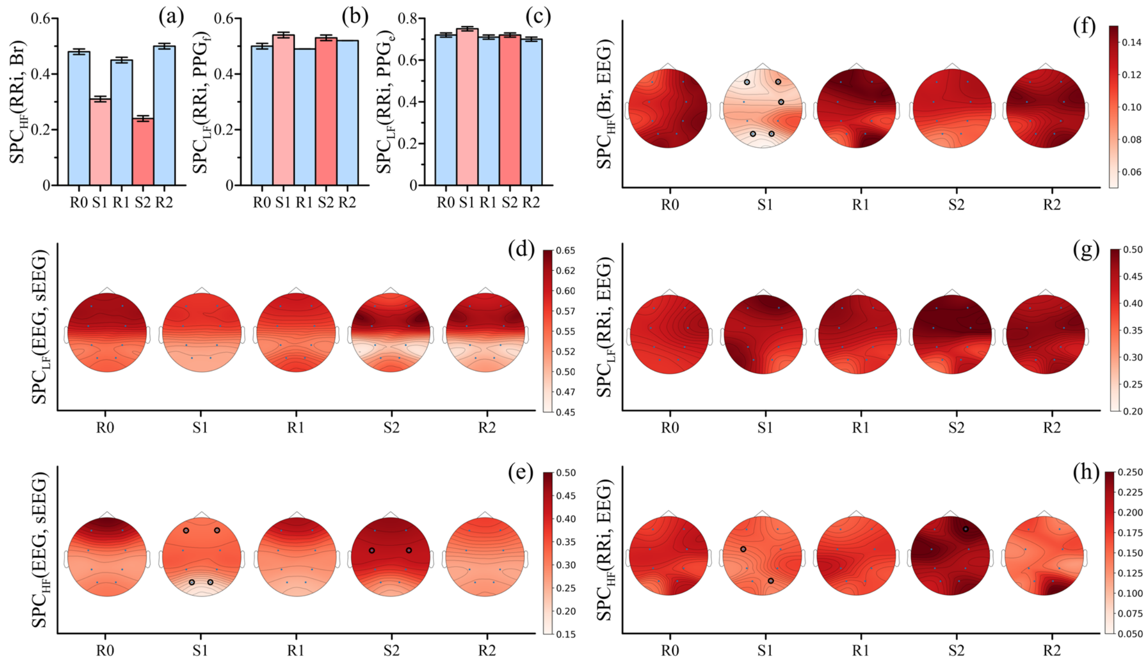


**Fig. 4** Mean values and their standard error for the following indices: (**a**) $SPC_{HF}$(RRi, Br), (**b**) $SPC_{LF}$(RRi, $PPG_f$), and (**c**) $SPC_{LF}$(RRi, $PPG_e$). Specific phase coherence in different brain areas for the following pairs of signals: (**d**) $SPC_{LF}$(EEG, sEEG), (**e**) $SPC_{HF}$(EEG, sEEG), (**f**) $SPC_{HF}$(EEG, Br), (**g**) $SPC_{LF}$(RRi, EEG), and (**h**) $SPC_{HF}$(RRi, EEG). The black circles mark the EEG leads, for which the mean value of spectral indices at the stages S1 and S2 is significantly different from the stages R1 and R2, respectively (according to the Mann–Whitney $U$-test at $p < 0.05$)

found no evidences of significant changes in the LF range (Fig. 4d). However, in the HF range the coherence between the F3–F4 and O1–O2 pairs of leads is significantly lower during the S1 stage, and the coherence between the C3 and C4 leads increases during the S2 stage (Fig. 4e). This can be related to the respiratory control centers projecting its activity onto the EEG signals. This hypothesis is indirectly supported by the significant decrease in the coherence between the respiratory signals and the same EEG leads during the S1 stage (Fig. 4f). The cardiorespiratory coupling can also be the reason of the significant decrease in coherence between the HF-oscillations in the C3 and O2 EEG leads and RRi during the S1 stage, and significant increase in coherence between the HF-oscillations in the F4 lead and RRi during the S2 stage (Fig. 4h). At the same time, we detected no response to the cognitive task when analyzing the coherence between the EEG leads and RRi (Fig. 4g).

In addition to the aforementioned indices, we also estimated a number of other indices based on the spectral analysis and phase coherence analysis. Some of them were sensitive to the cognitive tests, but the group-averaged changes were not statistically significant. The results related to these indices are shown in the supplementary material in Table S1.

The group-averaged values of the $SPC_{HF}$(RRi, Br) and nHF-EEG indices showed the most prominent and statistically significant response to the cognitive task. To study the sensitivity and specificity of these indices for the detection of stress, we performed the ROC-analysis and estimated the threshold values of indices. If the value of the index for a particular volunteer was lower than the threshold value, then the volunteer was considered to be in a stress state caused by a cognitive task. To plot the ROC-curves, we checked all threshold values from the smallest to the largest values of the indices with the step of 1%. For each threshold value, we calculated the amount of true positive results (TPR) and false positive results (FPR) when classifying the presence of stress. The ROC-curves constructed separately for the stages S1 and S2 are shown in Fig. 5 for both the $SPC_{HF}$(RRi, Br) and nHF-EEG indices.

Figure 5a shows the sensitivity and specificity of classification when using the $SPC_{HF}$(RRi, Br) index for the stages S1 and S2. The AUC's were 0.68 for the S1 stage and 0.74 for the S2 stage, showing that this index is better for detection of stress caused by the MT test. The black dots on the ROC-curves mark the points closest to the coordinates (0.0, 1.0). Such points are often used to determine the threshold value that offers the optimal combination of sensitivity and specificity. For the S1 stage, the threshold value of the $SPC_{HF}$(RRi, Br) index was 0.38 with TPR = 0.60 and FPR = 0.30. For the S2 stage, the threshold value of the $SPC_{HF}$(RRi, Br) index was 0.31 with TPR = 0.73 and FPR = 0.27.

Similarly, Fig. 5b shows the sensitivity and specificity of classification when using the nHF-EEG index during the stages S1 and S2. The AUC's were 0.70 for the S1

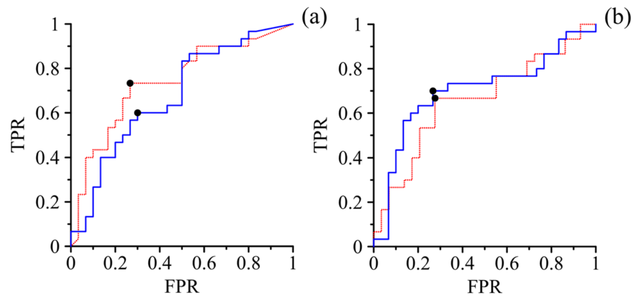


**Fig. 5** ROC-curves calculated when using the $SPC_{HF}$(RRi, Br) index (**a**) and nHF-F4 index (**b**) to detect the stress caused by the cognitive task. Blue lines are for the SCWT (stage S1 of the experiments) cognitive test. Red lines are for the MT cognitive test (stage S2 of the experiments). The black circles mark the points of ROC-curves closest to the (0, 1) coordinates

stage and 0.66 for the S2 stage, i.e. this index was somewhat better than $SPC_{HF}$(RRi, Br) index when detecting the stress caused by the SCWT. The threshold values of the nHF-EEG index for the S1 and S2 stages were 9.4% (TPR = 0.70 and FPR = 0.27) and 15.2% (TPR = 0.67 and FPR = 0.28). The corresponding points on the ROC-curves are marked by black circles (Fig. 5b).

Therefore, when detecting the stress caused by SCWT and MT tests, the nHF-EEG and $SPC_{HF}$(RRi, Br) indices complement each other. The nHF-EEG showed better results during the S1 stage, while the $SPC_{HF}$(RRi, Br) index showed better results during the S2 stage.

Table S2 in the Supplementary materials section shows the ROC-curves for other indices. However, they all show smaller sensitivity and specificity comparing to the nHF-EEG and $SPC_{HF}$(RRi, Br) indices.

## 5 Discussion

The aim of our study was to find reliable, objective, and quantitative indices for the detection of stress. We analyzed the indices related to the autonomic nervous system [1]. The obtained results may allow one to better understand the physiological reaction to stress, the dynamics of various systems generating infra-slow brain potentials, LF and HF oscillations in the PPG, RRi, and respiratory signals, and their interaction.

When designing the experiments, we followed the conclusions made in the review paper [2]. This review states that the SCWT and MT tests are the most effective and wide-spread stress tests [2]. The analysis of indices used in other studies [2] (Fig. 2) confirms that they respond to the changes in the psychophysiological state of the volunteers during the tests. However, the results were not statistically significant. This fact highlights the limited sensitivity of the existing indices and indicates that the development of new indices is still important. The analysis of respiratory signals, PPG, RRi, and infra-slow EEG potentials related to the autonomic control of circulation and respiratory system [52–55] are perspective sources of new sensitive indices. However, we found no relevant systematic studies.

Our results have shown that the integral power of HF-oscillations in the frontal lobe EEG leads significantly changes during the S1 and S2 stages of the experiment comparing to the control stages R0 and R1 (Fig. 3). This result can be explained by the projection of the activity of the autonomic control of respiration onto the EEG signals, since the HF-range corresponds to the typical frequency of respiration in a healthy human [51].

Cardiovascular coupling is another very important factor in the dynamics of the cardiovascular system and overall state of a subject [63–66]. It is well established that quantitative characteristics of the autonomic control activity can be used to detect the age-related changes [67, 68], different stages of sleep [68–71], predict the complications of various cardiovascular states [72–74], and advance the understanding of the cardiovascular and respiratory systems [75–77]. However, the nature of the cardiovascular coupling is complex, and biological systems demonstrate nonstationary behavior [75–77]. Therefore, the investigation of cardiovascular coupling requires application of sensitive nonlinear methods, geared towards noisy nonstationary data. We proposed a number of such specialized methods and used them to successfully detect coupling [55, 60, 69, 70, 78–80]. One of the indices, proposed in [60], was used to detect statistically significant changes in the psychophysiological state of the volunteers during the cognitive testing using the RRi and the signal of respiration (Fig. 4).

Figures 2–4 and Table S1 in the Supplementary information show the group-averaged values for a large set of indices during different stages of our experimental study, including periods of resting and cognitive task. The obtained data were used to select the indices, which not only give statistically significant results when classifying the psychophysiological state of the volunteer, but also provide the best sensitivity and specificity. The nHF-EEG and $SPC_{HF}$(RRi, Br) indices showed the best performance. For both indices, the sensitivity was about 0.7 with FPR close to 0.3. The nHF-EEG index showed better results when detecting the stress caused by the Stroop color word test, while the $SPC_{HF}$(RRi, Br) index was better for detecting the stress caused by the mental arithmetic test. Therefore, the nHF-EEG and $SPC_{HF}$(RRi, Br) indices complement each other. This can be explained by qualitatively different nature of these indices and information they provide.

The calculation of the proposed indices is based on the analysis of oscillations in the low-frequency range (less than 0.5 Hz) of biomedical signals. The registration of such signals requires a lower sampling frequency than the registration of oscillations having a higher frequency. Moreover, the measurement noise appears, as a rule, at much higher frequencies. Therefore, the proposed indices can be promising for using in lightweight wearable devices, such as smart-watches, capable of stress detection.

The fact that the interaction between the RRi, respiratory signal, and HF oscillations in EEG is affected by the cognitive task indicates the importance of further investigation of interactions between the central nervous systems and autonomic control of circulation.

## 6 Conclusion

We investigated the prospects of using the analysis of the LF and HF oscillations in the RRi, respiratory signals, PPG, and EEG to detect the changes in the pathophysiological state of healthy humans induced by performing the cognitive task. We compared the indices based on the power spectral analysis and estimation of the coherence between the pairs of signals. Overall, we estimated the group-averaged values for 144 indices for each stage of the experiment, which included the resting stages and the stages of cognitive task. ROC-analysis was performed for each index to determine its sensitivity and specificity when detecting the changes in the pathophysiological state.

According to the results of the ROC-analysis, the nHF-EEG and $\mathrm{SPC_{HF}}$(RRi, Br) indices have the best sensitivity and specificity among the tested indices. Both indices have sensitivity and specificity of 0.7 when using the optimal threshold values.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1140/epjs/s11734-022-00734-z.

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**Data availability** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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