

Kul'chyns'kyi Andriy B, Zukow Walery, Korolyshyn Tetyana A, Popovych Igor L. Interrelations between changes in parameters of HRV, EEG and humoral immunity at patients with chronic pyelonephritis and cholecystitis. *Journal of Education, Health and Sport*. 2017;7(9):439-459. eISSN 2391-8306. DOI <http://dx.doi.org/10.5281/zenodo.1001856>
<http://ojs.ukw.edu.pl/index.php/johs/article/view/4933>

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26.01.2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306

© The Author (s) 2017.

This article is published with open access at License: Open Access Journal Systems of Kazimierz Wielki University in Bydgoszcz, Poland
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non Commercial License

(<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.
This is an open access article licensed under the terms of the Creative Commons Attribution Non Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted, non commercial

use, distribution and reproduction in any medium, provided the work is properly cited.
The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.09.2017. Revised: 10.09.2017. Accepted: 10.09.2017.

INTERRELATIONS BETWEEN CHANGES IN PARAMETERS OF HRV, EEG AND HUMORAL IMMUNITY AT PATIENTS WITH CHRONIC PYELONEPHRITIS AND CHOLECYSTITIS

Andriy B Kul'chyns'kyi^{1,2}, Walery Zukow³, Tetyana A Korolyshyn⁴, Igor L Popovych⁴

¹Communal Hospital, Truskavets', Ukraine akul@i.ua

²Ukrainian Scientific Research Institute of Transport Medicine, Odesa

³Nicolaus Copernicus University, Torun', Poland zukow@wp.pl

⁴Department of Immunophysiology, OO Bohomolets' Institute of Physiology, Kyiv, Ukraine
i.popovych@biph.kiev.ua

Abstract

Background. The immunological homunculus conception considers somatotopic organization to CNS regulation of immune system. Previously, we have shown within the immunological homunculus conception that take place causal relationships parameters of EEG and HRV, on the one hand, and the parameters of cellular and humoral immunity as well as phagocytose, on the other hand. The purpose of this study is to find out the relationships between induced by balneotherapy **changes** in parameters of EEG and HRV, on the one hand, and the parameters of immunity, on the other hand. **Methods.** In basal conditions in 33 men and 10 women with chronic pyelonephritis and cholecystitis in remission, we recorded twice, before and after balneotherapy at the spa Truskavets', EEG ("NeuroCom Standard") and HRV ("Cardiolab+VSR"). In blood estimated routine parameters of Humoral Immunity on a set of I and II levels recommended by the WHO. **Results.** We detected that changes in relative level CD22⁺ B-Lymphocytes upregulated by parasympathetic outflows and β -rhythm generating structures that are projected onto the loci O2, Fp1, F3 and F4, while downregulated by sympathetic outflows and θ -rhythm generating structures that are projected onto the locus T5. Serum level of IgA upregulated by parasympathetic outflows and α -rhythm generating structures that are projected onto the loci T3 and C3 as well as δ -rhythm generating structures onto F7 and T5, while downregulated by sympathetic outflows and θ -rhythm generating structures that are projected onto the loci T5, F7, Fp2, F3, F8 and F4. Serum level of CIC upregulated by parasympathetic outflows and α -rhythm generating structures that are projected onto the loci T4, Fp2, T3, F8 and C3 as well as θ -rhythm generating structures onto the loci T3 and T6, while downregulated by sympathetic outflows and β -rhythm generating structures that are projected onto the loci Fp1, F3 and P4 as well as δ -rhythm generating structures onto T4. Unlike the previous parameters serum level of IgM downregulated by parasympathetic outflows and α -rhythm generating structures that are projected onto the loci T3 and T6 as well as β -rhythm generating structures onto the locus T5, while upregulated by sympathetic outflows and θ -rhythm generating structures that are projected onto the loci

F3, Fp2, T5, F4, O1 and F8. Serum level of IgG downregulated by parasympathetic outflows, while upregulated by sympathetic outflows and δ -rhythm generating structures that are projected onto the loci O2 and F8 as well as α -rhythm generating structures onto C3. **Conclusion.** The results are supplemented and refined Tracey's immunological homunculus conception.

Keywords: HRV, EEG, B-Lymphocytes, Immunoglobulines M,G,A, Circulating immune complexes, correlations.

INRODUCTION

Previously, we have shown within the immunological homunculus conception [29] that blood level of Leukocytes and proportions of subset of Leukocytes (Leukocytogram) [16], Neutrophils phagocytic function [13,15] as well as proportions of subset of Lymphocytes and serum level Immunoglobulines M, G and A [14] subordinate modulation central and autonomic nervous systems. In this study we set a goal to analyze the causal relationships between **changes** in parameters of EEG and HRV, on the one hand, and the parameters of Immunity, on the other hand.

MATERIAL AND METHODS

The object of observation were 33 men and 10 women aged 24-70 years old, who came to the spa Truskavets' (Ukraine) for the treatment of chronic pyelonephritis combined with cholecystitis in remission. The survey was conducted twice, before and after balneotherapy.

We recorded electrocardiogram in II lead to assess the parameters of HRV [1,2,3-7] (software and hardware complex "CardioLab+HRV" production "KhAI-MEDICA", Kharkiv, Ukraine). For further analysis the following parameters heart rate variability (HRV) were selected. Temporal parameters (Time Domain Methods): the standart deviation of all NN intervals (SDNN), coefficient of variation (Cv), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater then 50 ms (pNN₅₀); heart rate (HR), the moda (Mo), the amplitude of moda (AMo), variational sweep (MxDMn) as well as triangulary index (TI). Spectral parameters (Frequency Domain Methods): spectral power density (SPD) bands of HRV - high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultra low-frequency (ULF, range 0,015÷0,003 Hz). Expectant as classical indexes: LF/HF, LFnu=100%•LF/(LF+HF) and Baevskiy's Stress Index (BSI=AMo/2•Mo•MxDMn) as well as Baevskiy's Activity Regulatory Systems (BARS) [1].

Then EEG recorded a hardware-software complex "NeuroCom Standard" (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref tassels on the ears. Among the options considered the average EEG amplitude (μ V), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%) as well as absolute (μ V²/Hz) and relative (%) SPD of basic rhythms: β (35÷13 Hz), α (13÷8 Hz), θ (8÷4 Hz) and δ (4÷0,5 Hz) in all loci, according to the instructions of the device. In addition, calculated Laterality Index (LI) for SPD each Rhythm using formula [20]:

$$LI, \% = \Sigma [200 \cdot (\text{Right} - \text{Left}) / (\text{Right} + \text{Left})] / 8$$

We calculated also for HRV and each locus EEG the Entropy (h) of normalized SPD using formula C Shannon [cit. by: 22]:

$$hHRV = - [SPD_{HF} \cdot \log_2 SPD_{HF} + SPD_{LF} \cdot \log_2 SPD_{LF} + SPD_{VLF} \cdot \log_2 SPD_{VLF} +$$

+ SPD ULF•log₂ SPD ULF]/log₂ 4

hEEG= - [SPD α •log₂ SPD α + SPD β •log₂ SPD β + SPD θ •log₂ SPD θ + SPD δ •log₂ SPD δ]/log₂ 4

Immune status evaluated on a set of I and II levels recommended by the WHO. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD8, CD22 and CD16 from company "Granum" (Kharkiv) with visualization under light microscope with immersion system. Subpopulation of T cells with receptors high affinity determined by test of "active" rosette formation [17]. The state of humoral immunity judged by the concentration in serum of Immunoglobulins classes G, A, M (ELISA, analyser "Immunochem", USA) and circulating immune complexes (by polyethylene glycol precipitation method) [17].

Results processed by methods of correlation and canonical analyses, using the software package "Statistica 5.5".

RESULTS AND DISCUSSION

In this article, we will analyze the relationships between changes in parameters of EEG and HRV, on the one hand, and the parameters of **humoral** immunity only, on the other hand. Cellular immunity and phagocytosis will be the subject of following articles. A separate fragment is published in abstract format [12,24,25].

It is known that the connections between the nervous and immune systems are two-way. On the one hand, the nervous system, through its mediators (acetylcholine, norepinephrine, neuropeptides), affects proliferation, apoptosis and the function of lymphocytes, macrophages and microphages expressing the corresponding receptors. On the other hand, immunocytes release cytokines, hormones and even the same neurotransmitters that together affect neuron activity [8-11,18,21-23,26]. Therefore, the nature of cause-effect relationships can not be unambiguous. Proceeding from this, purely arbitrarily, we will consider the changes in the parameters of HRV and EEG as a factor (argument), instead of changing the parameters of immunity as a productive feature (function).

First of all, we, using a canonical analysis, found out what factors of nervous regulation and to what extent influence changes in the proportion of subset of B-lymphocytes in blood.

Unfortunately, because of the total lack of funding, in our cheap "NeuroCom Standard" device function "Thomography" is not involved, so we can not surely judge the localization of nerve structures that are projected onto those or other loci.

As can be seen from Table 1, the canonical root of nerve regulation receives predominantly **negative** factor loadings that reflect the **stimulating** effect on B-lymphocytes blood level by the side of HRV markers of vagal tone as well as β -rhythm generating structures that are projected onto the right occipitalis and medialis frontalis as well as left anterior and medialis frontalis loci as well as θ -rhythm generating structures that are projected onto the left anterior temporalis locus.

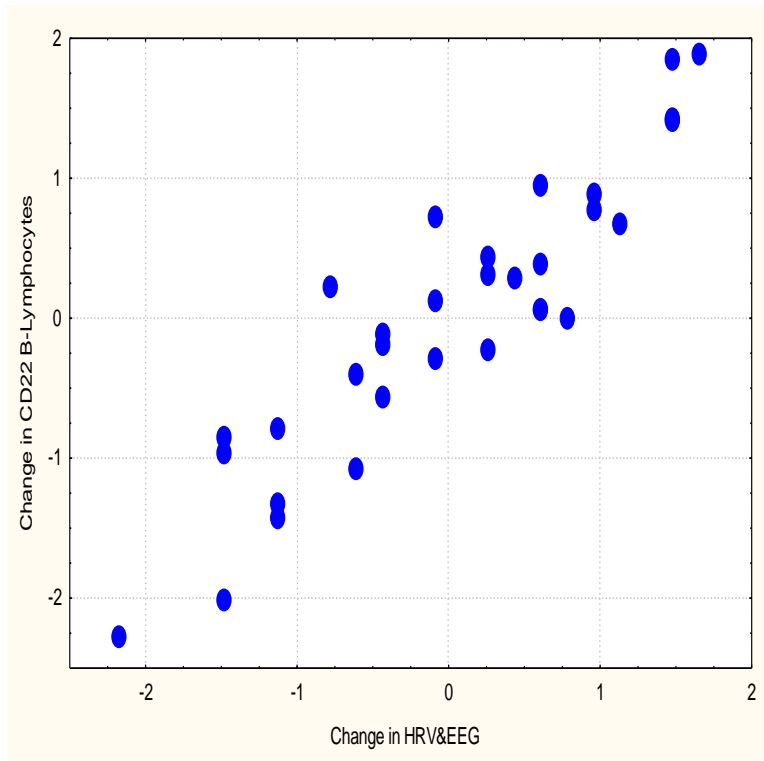
Table 1. Factor structure of canonical Roots representing Neural parameters and CD22⁺ B-lymphocytes blood level

Right set	R
Cv HRV, %	-,444
SDNN HRV, ms	-,430
ULF HRV SPD, ms ²	-,390
VLF HRV SPD, ms ²	-,389
MxDMn HRV, ms	-,359
Bayevskiy Stress Index, ln	,406
AMo HRV, %	,397
O2-β SPD, %	-,459
Fp1-β SPD, %	-,345
T3-θ SPD, %	-,338
F4-β SPD, μV ² /Hz	-,322
F3-β SPD, %	-,315
α-Rhythm deviation, Hz	-,393
C3 Entropy	-,391
T5-θ SPD, %	,275
β-Rhythm Asymmetry, %	,319
β-Rhythm Index, %	,294
θ-Rhythm Frequency, Hz	,258
Left set	R
CD22 ⁺ B-Lymphocytes, %	-1

It is speculated that ULF band (0,015÷0,003 Hz) associated with oscillation blood level of norepinephrine (0,002 Hz) as well as 17-OCS (0,0019 Hz) [cit by: 7], while VLF band HRV (0,04÷0,015 Hz) associated with oscillation blood levels of renin (0,04 Hz) and epinephrine (0,025 Hz), reflects thermoregulatory cycles [cit by: 2,7], cerebral ergotropic and metabolotropic outflows [cit by: 1], activation of cerebral sympathetic-adrenal system [cyt by: 4], sympathetic activity [cit by: 6]. But in this study we found that changes in the SPD ULF as well as VLF bands positively correlates with changes in vagal markers MxDMn ($r=0,75$ and $0,77$), SDNN ($r=0,66$ and $0,88$) and RMSSD ($r=0,49$ and $0,74$ respectively), hence this parameter of HRV also reflects parasympathetic outflows.

Positive factor loadings reflect the **inhibiting** effect on B-lymphocytes blood level by the side of HRV markers of sympathetic tone and θ-rhythm generating structures that are projected onto the left posterior temporalis locus. In addition, stimulating effect makes Deviation (variability) of α-rhythm and Entropy of relative SPD of the rhythms in the locus C3, which is probably projected the left hippocampus [27], while inhibiting effect makes Asymmetry and Index of β-rhythm as well as Frequency of θ-rhythm.

Judging by the coefficient of canonical correlation, changes in the nervous regulation determine changes in the level of B-lymphocytes by 84,4% (Fig. 1).



$R=0,919$; $R^2=0,844$; $\chi^2_{(18)}=39$; $p=0,003$; $\Lambda \text{ Prime}=0,156$

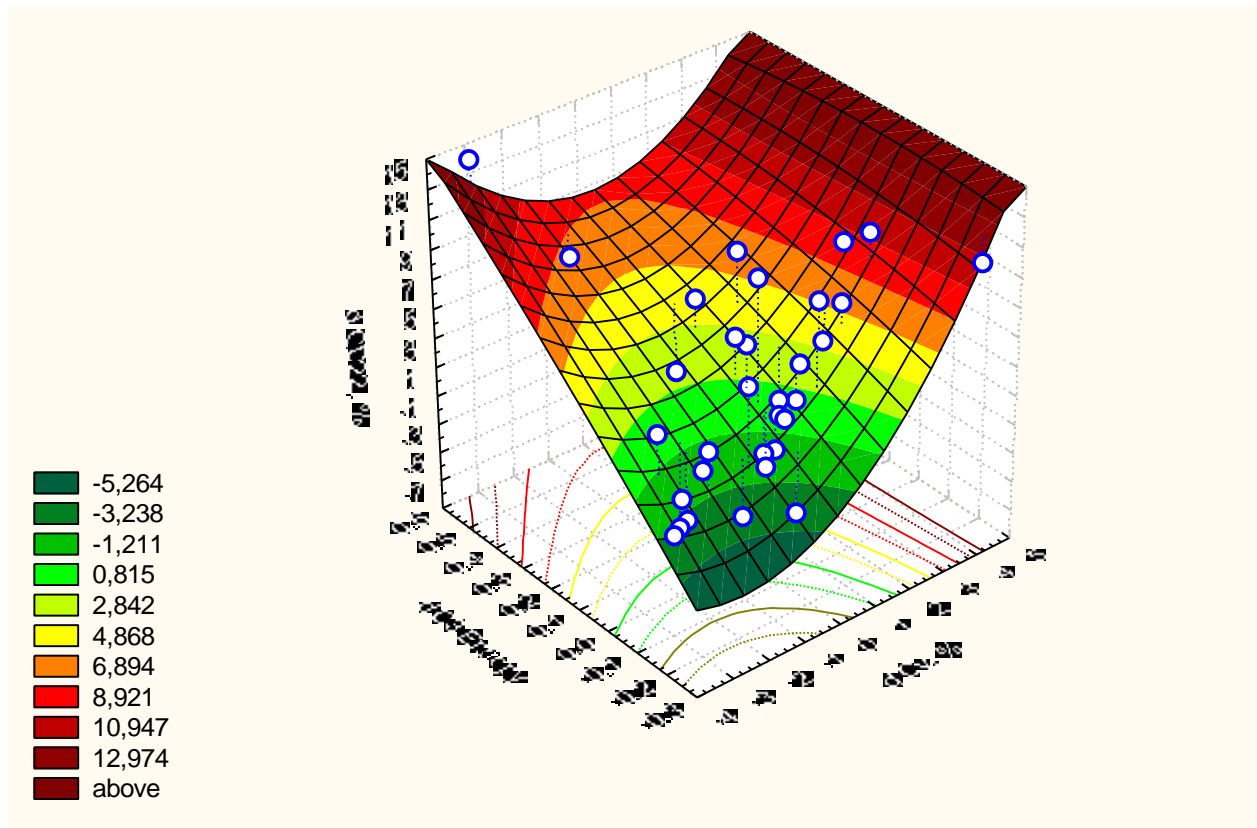
Figure 1. Canonical correlation between changes in parameters of HRV and EEG (line X) and blood CD22⁺ B-lymphocytes level (line Y)

Among mentioned parameters HRV and EEG a regression model with stepwise exclusion included the following 9 only (Table 2).

Table 2. Regression Summary for Dependent Variable: change in CD22 B-Lymphocytes
 $R=0,893$; $R^2=0,798$; Adjusted $R^2=0,727$; $F_{(8,2)}=11,3$; $p<10^{-5}$; SE of estimate: 3,0%

		Beta	St. Err. of Beta	B	St. Err. of B	n=32 $t_{(23)}$	p-level
Change in Variables	r		Intercept	1,855	,570	3,25	,004
Cv HRV, %	0,41	,279	,102	,891	,325	2,74	,012
C3 Entropy	0,36	,375	,109	12,47	3,63	3,43	,002
α -Rhythm Deviation, Hz	0,36	,296	,097	2,748	,903	3,04	,006
T3- θ SPD, %	0,31	,378	,108	,444	,127	3,50	,002
F4- β SPD, $\mu V^2/Hz$	0,30	,206	,097	,035	,016	2,13	,044
β -Rhythm Index, %	-0,27	-,317	,101	-,104	,033	-3,14	,005
T5- θ SPD, %	-0,25	-,459	,101	-,454	,100	-4,54	,0001
θ -Rhythm Frequency, Hz	-0,24	-,263	,101	-,932	,359	-2,60	,016

Fig. 2 visualizes the dependence of changes in the level of B-lymphocytes on changes in the tone of the Vagus and the Entropy of the rhythms in the locus C3.



$$dCD22 (\%) = 1,71 + 1,55 \cdot dCv(\%) + 14,8 \cdot dC3h$$

$$R = 0,599; R^2 = 0,359; \text{Adjusted } R^2 = 0,314; F_{(2,3)} = 8,1; p = 0,002; \text{SE of estimate: } 4,8\%$$

Figure 2. Interrelations between changes in coefficient of variation HRV (line X), rhythms entropy in locus C3 (line Y) and CD22⁺ B-lymphocytes blood level (line Z)

Factor structure of canonical Roots representing Neural parameters and IgM serum level (Table 3) testifies that the latter **downregulated** by parasympathetic outflows as well as α - and θ -rhythm generating structures that are projected onto the left anterior temporalis locus as well as β -rhythm generating structures projected onto left posterior temporalis locus and α -rhythm generating structures projected onto right posterior temporalis locus, which all probably reflects the amygdala [27], while **upregulated** by sympathetic outflows and θ -rhythm generating structures that are projected onto the 12 loci.

In addition, inhibiting effect makes Entropy of bands HRV, while stimulating effect makes Entropy of the rhythms in 7 loci.

In total, changes in the nervous regulation determine changes in the level of IgM by 97,2% (Fig. 3).

Table 3. Factor structure of canonical Roots representing Neural parameters and IgM level

Right set	R
ULF HRV SPD, ms ²	,539
ULF HRV SPD, %	,463
HRV SPD Entropy	,355
MxDMn HRV, ms	,306
LF HRV SPD, %	-,293
T3- α SPD, %	,354
T3- α SPD, $\mu\text{V}^2/\text{Hz}$,341
T3- θ SPD, $\mu\text{V}^2/\text{Hz}$,311
T5- β SPD, $\mu\text{V}^2/\text{Hz}$,340
T6- α SPD, $\mu\text{V}^2/\text{Hz}$,327
F3- θ SPD, %	-,477
Fp2- θ SPD, %	-,469
T5- θ SPD, %	-,433
F4- θ SPD, %	-,422
O1- θ SPD, %	-,409
F8- θ SPD, %	-,390
C4- θ SPD, %	-,367
C3- θ SPD, %	-,363
P4- θ SPD, %	-,348
F7- θ SPD, %	-,340
T6- θ SPD, %	-,332
T4- θ SPD, %	-,313
Fp1 Entropy	-,345
P4 Entropy	-,331
F4 Entropy	-,329
F3 Entropy	-,431
C3 Entropy	-,397
F7 Entropy	-,381
Fp2 Entropy	-,373
Left set	R
IgM	-1

Among mentioned parameters HRV and EEG a regression model with stepwise exclusion included 12 only (Table 4).

Table 4. Regression Summary for Dependent Variable: change in IgM serum level
R=0,848; R²=0,719; Adjusted R²=0,541; F₍₁₂₎=4,0; p=0,003; SE of estimate: 0,26 g/l

		Beta	St. Err. of Beta	B	St. Err. of B	n=32 t ₍₁₉₎	p-level
Change in Variables	r		Intercept	,0438	,0596	0,73	,471
ULF HRV, ms ²	-0,53	-,304	,165	-,0006	,0003	-1,84	,081
T6-α SPD, μV ² /Hz	-0,32	-,594	,293	-,0017	,0008	-2,02	,057
T5-α SPD, μV ² /Hz	-0,30	-,407	,319	-,0010	,0008	-1,28	,217
Fp2-α SPD, μV ² /Hz	-0,26	,587	,358	,0024	,0014	1,64	,117
F3-θ SPD, %	0,47	,228	,236	,0089	,0092	0,97	,346
F3 Entropy	0,43	,250	,221	,6789	,5995	1,13	,272
O1-θ SPD, %	0,40	,376	,148	,0314	,0124	2,54	,020
F8-θ SPD, %	0,39	,418	,223	,0211	,0113	1,87	,077
C4-θ SPD, %	0,36	-,441	,245	-,0241	,0133	-1,80	,087
T6 Entropy	0,31	-,306	,208	-,5834	,3969	-1,47	,158
δ-Rhythm Laterality, %	0,30	,259	,142	,0016	,0009	1,83	,083
LF HRV SPD, %	0,29	,172	,147	,0047	,0040	1,17	,255

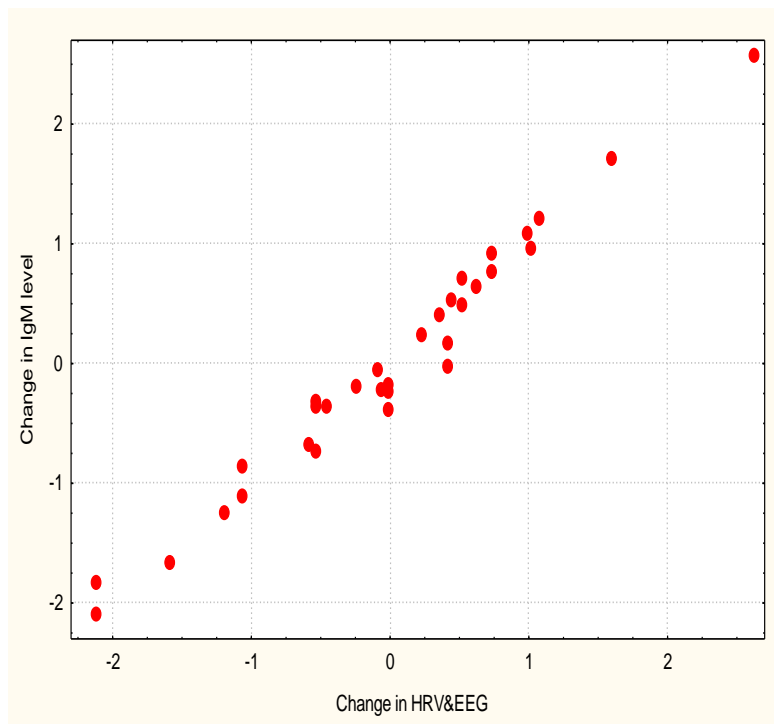


Figure 3. Canonical correlation between changes in parameters of HRV and EEG (line X) and serum IgM level (line Y)

In Fig. 4-6, the closest partial neuro-immune interrelations are visualized.

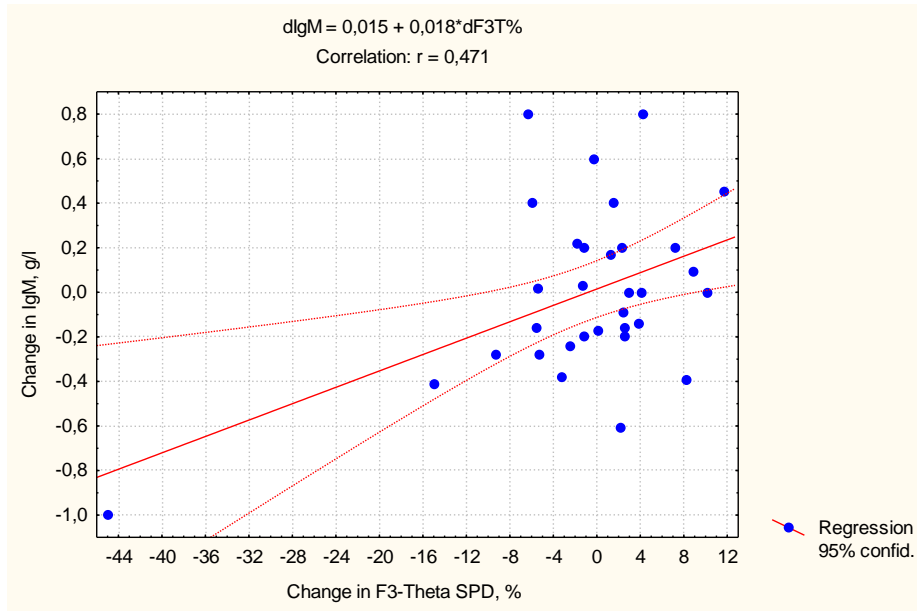


Figure 4. Relationship between changes in relative SPD of θ -rhythm in locus F3 (line X) and serum IgM level (line Y)

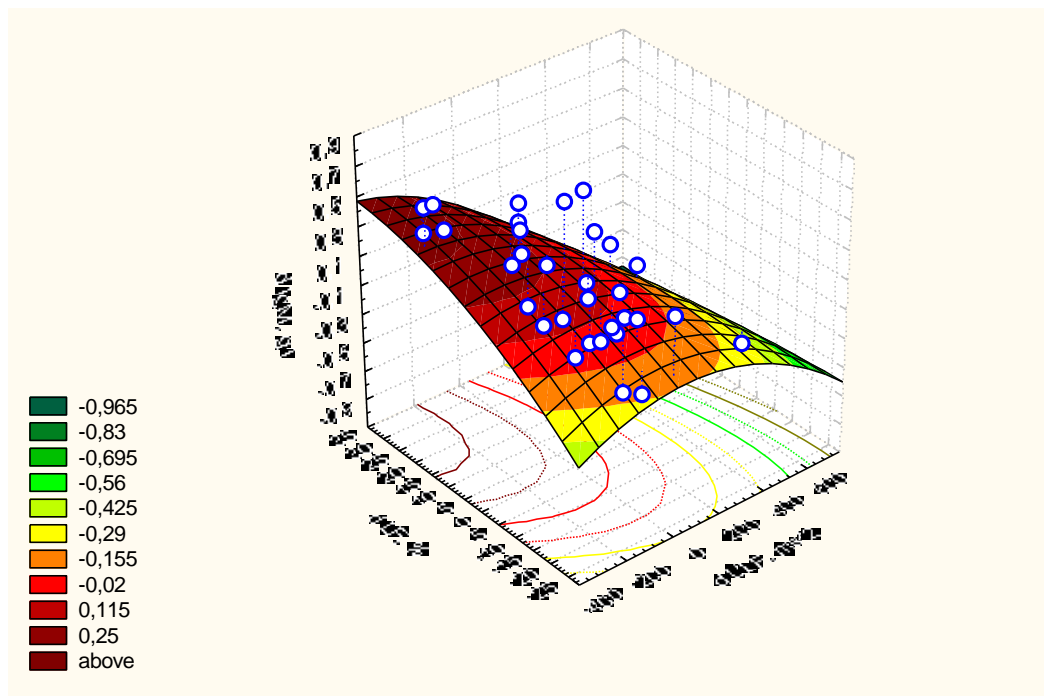
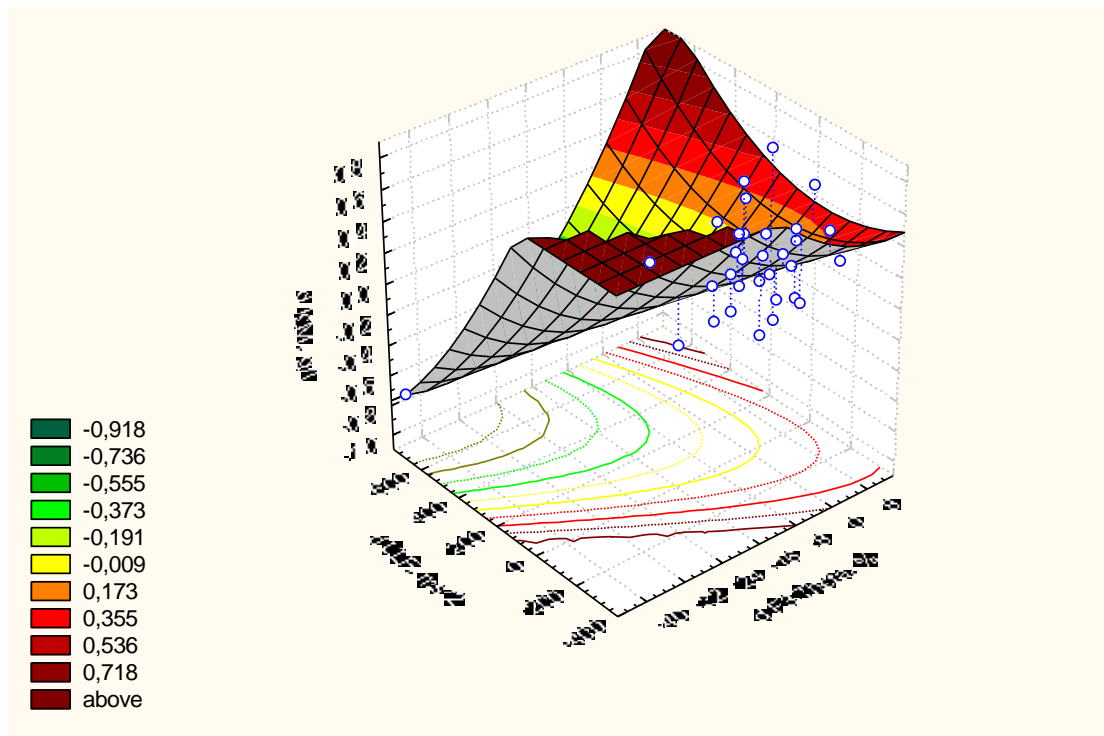


Figure 5. Interrelations between changes in absolute SPD ULF band HRV (line X), relative SPD LF band HRV (line Y) and serum IgM level (line Z)



$$dIgM(g/l)=0,010+0,0097 \cdot dF3-0(\%)-0,0008 \cdot dULF(ms^2)$$

$R=0,569$; $R^2=0,323$; Adjusted $R^2=0,277$; $F_{(2,3)}=6,9$; $p=0,003$; SE of estimate: 0,33 g/l

Figure 6. Interrelations between changes in relative SPD 0-Rhythm in locus F3 (line X), absolute SPD ULF band HRV (line Y) and serum IgM level (line Z)

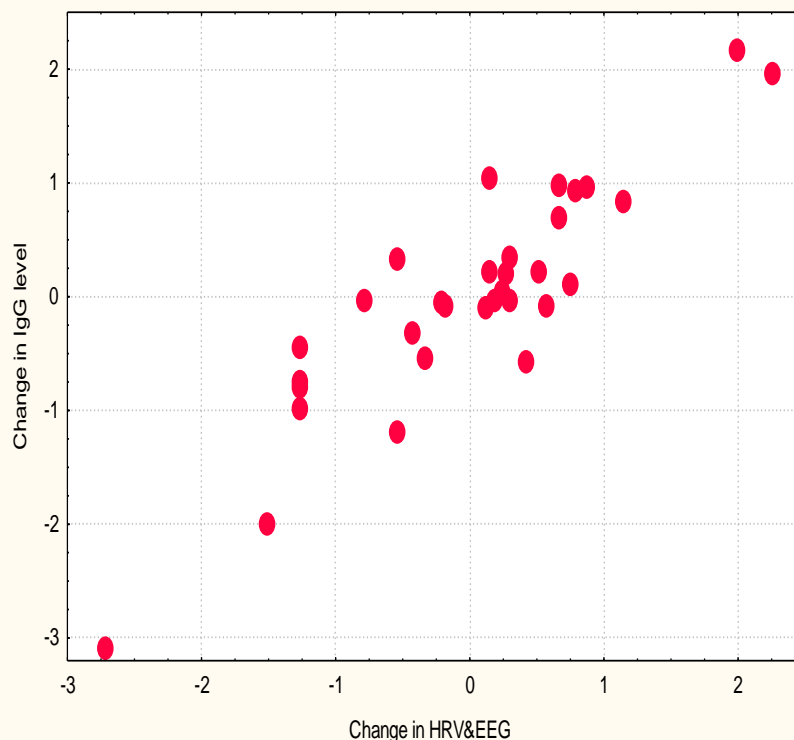
Serum level of IgG **downregulated** by parasympathetic outflows, while **upregulated** by sympathetic outflows.

Table 5. Factor structure of canonical Roots representing Neural parameters and IgG serum level

Right set	R
Moda HRV, ms	,310
HR, beats/min	-,300
HF HRV SPD, %	,304
AMo/Mo HRV, units	-,291
θ -Rhythm Index, %	,680
β -Rhythm Frequency, Hz	,502
δ -Rhythm Deviation, Hz	,389
α -Rhythm Frequency, Hz	,338
C4 Entropy	,361
O1 Entropy	,342
T5 Entropy	,301
T6 Entropy	,290
O2- δ SPD, $\mu V^2/Hz$	-,462
F8- δ SPD, $\mu V^2/Hz$	-,341
δ -Rhythm Asymmetry, %	-,301
C3 α SPD, %	-,378
Left set	R
IgG	-1

In addition, a decrease in IgG levels is associated with an increase in θ -rhythm Index, α - and β -rhythms Frequency and δ -rhythm Deviation as well as in Entropy of relative SPD of rhythms in loci C4, O1, T5 and T6. In return, a increase in IgG levels is associated with an decrease in δ -rhythm Asymmetry and SPD δ -rhythm generating structures that are projected onto the loci O2 and F8 as well as α -rhythm generating structures onto locus C3.

Changes in the nervous regulation determine changes in the level of IgG by 80,0% (Fig. 7).



$R=0,894$; $R^2=0,800$; $\chi^2_{(16)}=35$; $p=0,004$; $\Lambda \text{ Prime}=0,200$

Figure 7. Canonical correlation between changes in parameters of HRV and EEG (line X) and serum IgG level (line Y)

Among mentioned parameters HRV and EEG a regression model with stepwise exclusion included 10 only (Table 6).

Table 6. Regression Summary for Dependent Variable: change in IgG serum level
 $R=0,876$; $R^2=0,767$; Adjusted $R^2=0,656$; $F_{(10,2)}=6,9$; $p=10^{-4}$; SE of estimate: 1,98 g/l

		Beta	St. Err. of Beta	B	St. Err. of B	n=32 $t_{(21)}$	p-level
Change in Variables	r		Intercpt	,118	,435	0,27	,789
θ -Rhythm Index, %	-0,61	-,301	,134	-,023	,010	-2,25	,035
β -Rhythm Frequency, Hz	-0,45	-,360	,130	-,220	,079	-2,77	,012
δ -Rhythm Deviation, Hz	-0,35	-,178	,135	-1,510	1,143	-1,32	,201
HF HRV SPD, %	-0,27	-,319	,117	-,132	,048	-2,73	,013
T5 Entropy	-0,27	,248	,189	3,823	2,901	1,32	,202
T6 Entropy	-0,26	,266	,159	4,435	2,655	1,67	,110
O2- δ SPD, $\mu V^2/Hz$	0,41	1,155	,382	,0031	,0010	3,02	,006
C3 α SPD, %	0,34	,136	,118	,037	,032	1,16	,260
F8- δ SPD, $\mu V^2/Hz$	0,31	-,737	,306	-,0044	,0018	-2,41	,025
δ -Rhythm Asymmetry, %	0,27	,413	,126	,043	,013	3,28	,004

The most noticeable modulates the level of IgG Index of θ -rhythm (Fig. 8).

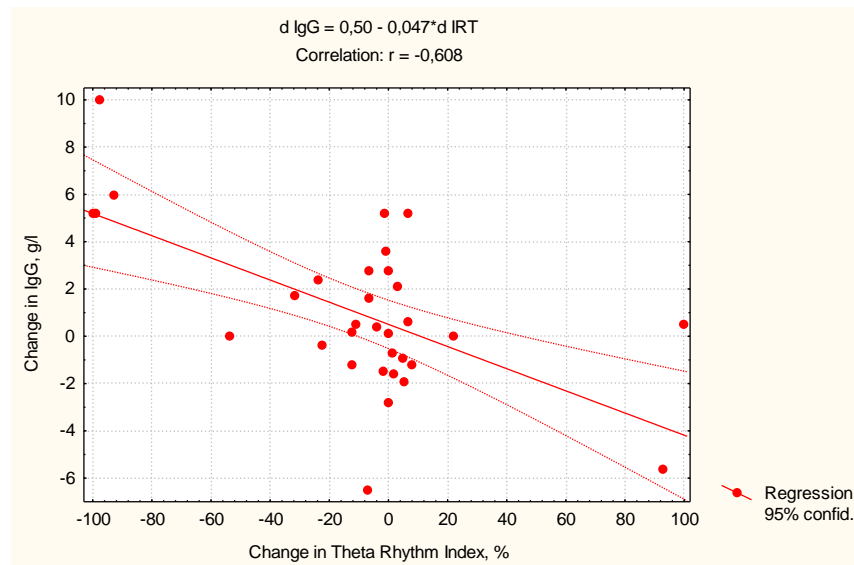


Figure 8. Relationship between changes in θ -rhythm index (line X) and serum IgG level (line Y)

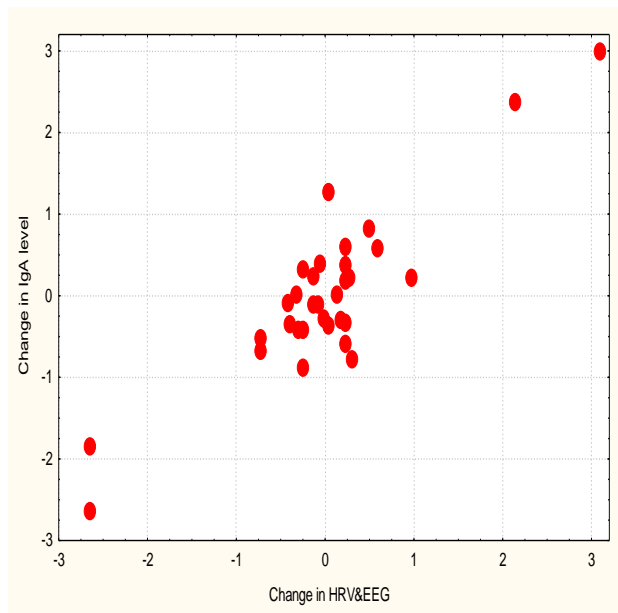
Factor structure of canonical Roots representing Neural parameters and IgA serum level (Table 7) testifies that the latter **upregulated** by parasympathetic outflows as well as δ -rhythm generating structures that are projected onto the left frontalis lateralis and temporalis posterior loci as well as α -rhythm generating structures are projected onto left temporalis anterior and centralis loci, and Index of β -rhythm.

Table 7. Factor structure of canonical Roots representing Neural parameters and IgA level

Right set	R
ULF HRV SPD, ms ²	-,550
F7- δ SPD, $\mu\text{V}^2/\text{Hz}$	-,495
T5- δ SPD, $\mu\text{V}^2/\text{Hz}$	-,492
T3- α SPD, %	-,421
C3- α SPD, %	-,402
β -Rhythm Index, %	-,391
θ -Rhythm Index, %	,514
T5- θ SPD, %	,533
F7- θ SPD, %	,464
Fp2- θ SPD, %	,452
F3- θ SPD, %	,416
F8- θ SPD, %	,416
F4- θ SPD, %	,414
T5 Entropy	,625
F7 Entropy	,571
T6 Entropy	,529
O1 Entropy	,519
Fp2 Entropy	,472
F8 Entropy	,466
Left set	R
IgA	-1

Instead, a **decrease** in IgA level is associated with an **increase** in the θ -rhythm Index and its SPD in 6 loci as well as in Entropy of relative SPS of rhythms in 6 loci.

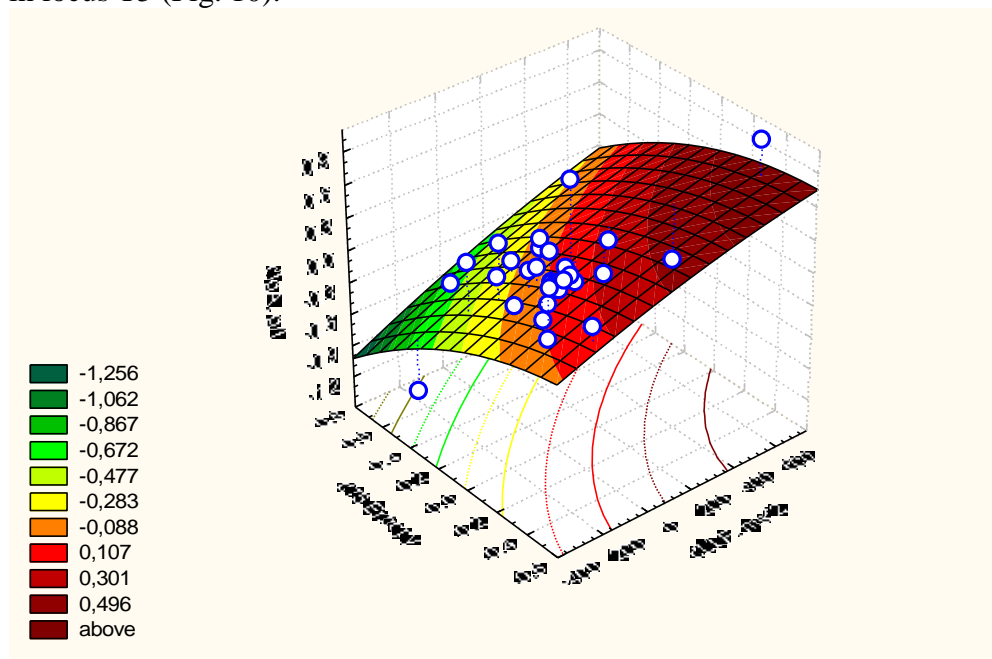
In total, changes in the nervous regulation determine changes in the level of IgA by 79,1% (Fig. 9).



$$R=0,889; R^2=0,791; \chi^2_{(19)}=32; p=0,031; \Lambda \text{ Prime}=0,209$$

Figure 9. Canonical correlation between changes in parameters of HRV and EEG (line X) and serum IgA level (line Y)

The IgA level is most modulated by SPD ULF band HRV and Entropy PSD of rhythms EEG in locus T5 (Fig. 10).



$$d\text{IgA}(\text{g/l})=-0,080+0,0008 \cdot d\text{ULF}(\text{ms}^2)-0,873 \cdot d\text{T5 entropy}$$

$$R=0,651; R^2=0,424; \text{Adjusted } R^2=0,384; F_{(2,3)}=10,7; p<10^{-3}; \text{SE of estimate: } 0,33 \text{ g/l}$$

Figure 10. Interrelations between changes in absolute SPD ULF band HRV (line X), rhythms entropy in locus T5 (line Y) and serum IgA level (line Z)

Among mentioned parameters HRV and EEG a regression model with stepwise exclusion included 9 only (Table 8).

Table 8. Regression Summary for Dependent Variable: change in IgA serum level
R=0,876; R²=0,768; Adjusted R²=0,673; F_(9,2)=8,1; p<10⁻⁴; SE of estimate: 0,24 g/l

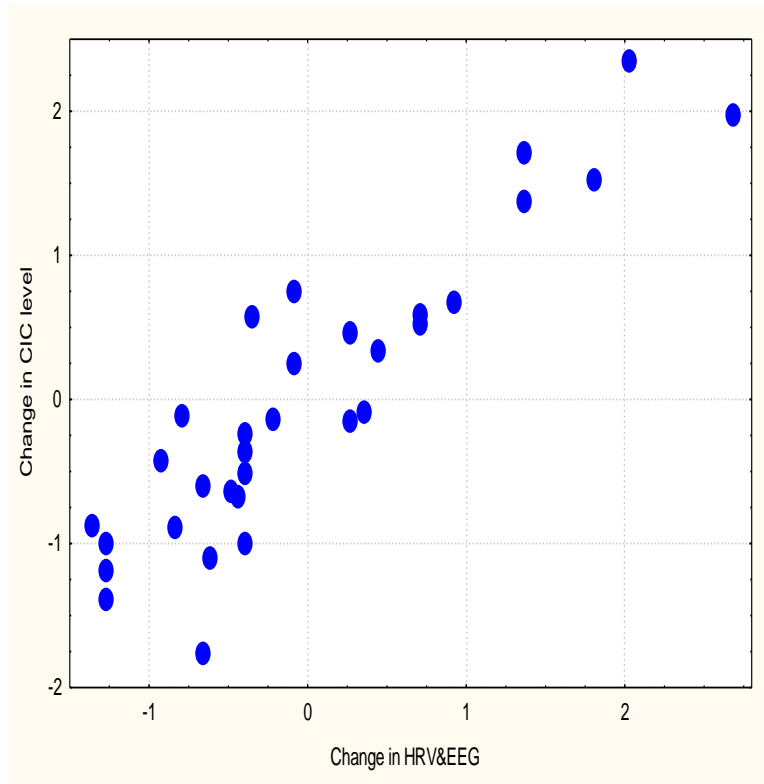
		Beta	St. Err. of Beta	B	St. Err. of B	n=32 t ₍₂₂₎	p-level
Change in Variables	r		Intercept	-,0826	,0486	-1,70	,103
F7 Entropy	-0,51	,473	,209	,9832	,4344	2,26	,034
O1 Entropy	-0,46	-,175	,137	-,3670	,2860	-1,28	,213
θ-Rhythm Index, %	-0,46	-,453	,121	-,0044	,0012	-3,74	,001
F7-θ SPD, %	-0,41	-,699	,186	-,0586	,0156	-3,76	,001
F8-θ SPD, %	-0,37	,193	,138	,0107	,0077	1,40	,176
ULF HRV SPD, ms ²	0,49	,391	,122	,0009	,0003	3,20	,004
T3-α SPD, %	0,37	,273	,117	,0065	,0028	2,33	,029
β-Rhythm Index, %	0,35	,416	,141	,0099	,0033	2,96	,007
VLF HRV SPD, %	0,28	,232	,122	,0057	,0030	1,90	,071

The last among the registered parameters of humoral immunity - circulating immune complexes – **downregulated** by sympathetic outflows as well as β-rhythm generating structures are projected onto right parietalis and left frontalis anterior and medialis loci as well as δ-rhythm generating structures are projected onto right temporalis anterior locus, while **upregulated** by parasympathetic outflows as well as θ- and α-rhythm generating structures are projected onto various loci (Table 9).

Table 9. Factor structure of canonical Roots representing Neural parameters and CIC serum level

Right set	R
$(MxDMn \cdot Mo)^{-1}$ HRV, units	,377
LF HRV SPD, %	,361
Heart Rate, beats/min	,336
Bayevskiy ARS Index, units	,328
Bayevskiy Stress Index, ln	,321
β -Rhythm Frequency, Hz	,346
P4- β SPD, %	,318
Fp1- β SPD, %	,313
F3- β SPD, %	,297
δ -Rhythm Laterality, %	,343
T4- δ SPD, %	,338
MxDMn HRV, ms	-,332
pNN ₅₀ , HRV, %	-,302
T3- θ SPD, %	-,430
T6- θ SPD, %	-,307
T4- α SPD, %	-,403
Fp2- α SPD, %	-,386
T3- α SPD, %	-,338
F8- α SPD, %	-,323
C3- α SPD, %	-,315
Left set	R
CIC	-1

In total, changes in the nervous regulation determine changes in the level of CIC by 82,1% (Fig. 11).



$R=0,906$; $R^2=0,821$; $\chi^2_{(20)}=34$; $p=0,023$; Λ Prime=0,179

Figure 11. Canonical correlation between changes in parameters of HRV and EEG (line X) and serum CIC level (line Y)

Among mentioned parameters HRV and EEG a regression model with stepwise exclusion included 7 only (Table 10).

Table 10. Regression Summary for Dependent Variable: change in CIC serum level
 $R=0,811$; $R^2=0,658$; Adjusted $R^2=0,559$; $F_{(7,2)}=6,6$; $p<10^{-3}$; SE of estimate: 15 units

		Beta	St. Err. of Beta	B	St. Err. of B	n=32 $t_{(24)}$	p-level
Change in Variables	r		Intercept	-,970	2,87	-0,34	,738
T3- θ SPD, %	0,39	,444	,140	2,064	,651	3,17	,004
T4- α SPD, %	0,36	-,329	,187	-,599	,341	-1,76	,092
MxDMn HRV, ms	0,30	,267	,133	,094	,047	2,01	,056
C3- α SPD, %	0,29	,354	,143	,656	,265	2,48	,021
F8- α SPD, %	0,29	,564	,173	,817	,251	3,26	,003
δ -Rhythm Laterality, %	-0,31	-,211	,130	-,078	,048	-1,63	,116
P4- β , %	-0,29	-,671	,141	-1,418	,298	-4,76	,0001

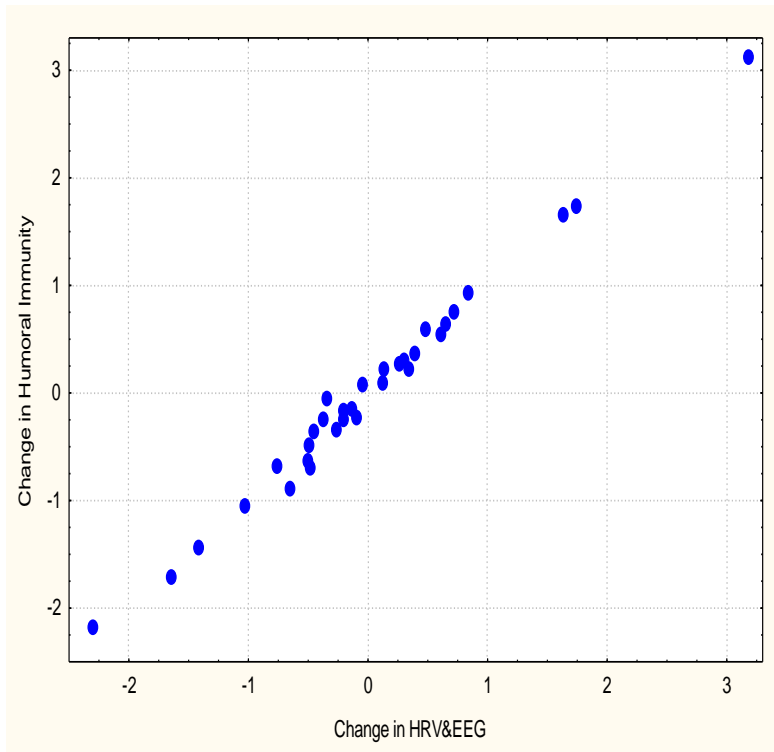
At the final stage, we analyzed the canonical correlation between changes in the parameters of the nerve regulation, on the one hand, and humoral immunity - on the other hand. The program identified two pairs of canonical roots (Table 11).

Table 11. Factor structure of canonical Roots representing Neural and Humoral Immune parameters

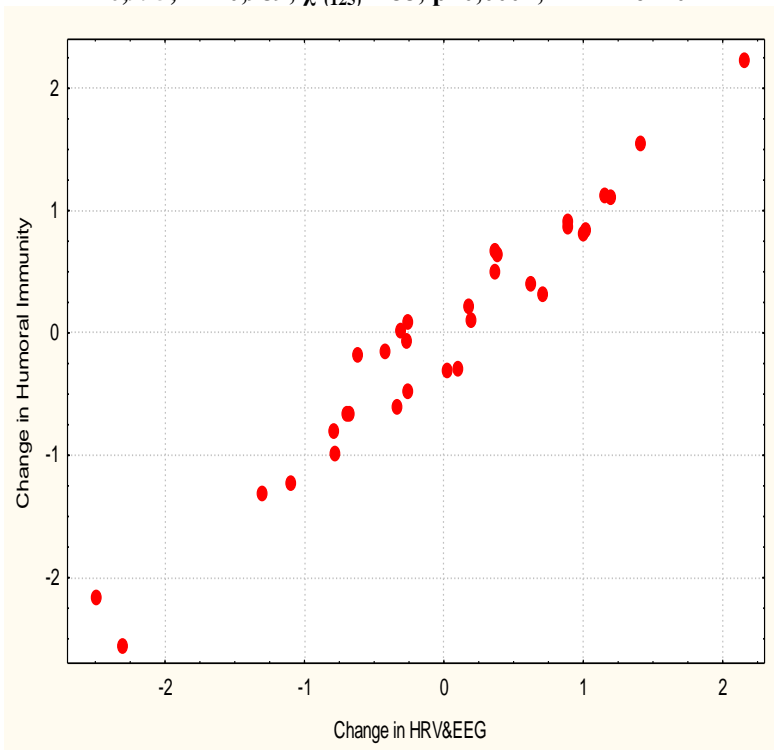
Right set	Root 1	Root 2
T5- θ SPD, %	-,543	-,292
F3- θ SPD, %	-,525	-,248
F7- θ SPD, %	-,516	-,168
F4- θ SPD, %	-,465	-,238
Fp2- θ SPD, %	-,451	-,341
F7 Entropy	-,340	-,341
AMo HRV, %	-,206	,167
ULF HRV SPD, ms ²	,508	,319
SDNN HRV, ms	,234	-,024
VLF HRV SPD, ms ²	,140	,093
O2- β SPD, %	,451	,072
O2- δ SPD, $\mu\text{V}^2/\text{Hz}$	-,062	,318
F7- δ SPD, $\mu\text{V}^2/\text{Hz}$	-,016	,115
β -Rhythm Frequency, Hz	,206	-,541
θ -Rhythm Index, %	,312	-,443
F8- θ SPD, %	-,226	-,467
O1- θ SPD, %	-,192	-,315
Fp2 Entropy	-,247	-,481
T6 Entropy	-,257	-,440
F3 Entropy	-,209	-,432
O1 Entropy	-,107	-,381
C3 Entropy	-,063	-,371
T5 Entropy	-,169	-,323
Left set	Root 1	Root 2
CD22	,572	,005
IgM	-,559	-,529
CIC	-,314	,284
IgG	-,468	,685
IgA	,170	,475

The neural root of the first pair receives **negative** factor loads from the relative SPD of θ -rhythm, which generates structures that are projected onto the left temporalis posterior, frontalis medialis and lateralis as well as right frontalis medialis and anterior loci as well as from sympathetic tone. Instead, **positive** factor loadings give a vagal tone and β -rhythm generating structures are projected onto right occipital locus. The immune root of the first pair receives positive factor loadings from the B-lymphocytes level, while negative loadings from IgM, CIC as well as IgG levels. Canonical correlation is very strong (Fig. 12, above).

The neural root of the second pair receives **positive** factor loadings from the δ -rhythm generating structures are projected onto right occipitalis and left frontalis lateralis loci while **negative** factor loads from the θ -rhythm generating structures that are projected onto the right frontalis lateralis and left occipitalis loci as well as from Index of θ -rhythm, Frequency of β -rhythm and Entropy of relative SPD of rhythms in various loci. The immune root of the second pair receives positive factor loadings from the IgG and IgA as well as CIC levels, while negative loadings from IgM level. Canonical correlation is very strong too (Fig. 12, below).



$R=0,995$; $R^2=0,989$; $\chi^2_{(125)}=188$; $p=0,0002$; $\Lambda \text{ Prime}<10^{-5}$



$R=0,974$; $R^2=0,949$; $\chi^2_{(96)}=118$; $p=0,066$; $\Lambda \text{ Prime}=0,0005$

Figure 12. Canonical correlation between changes in parameters of HRV and EEG (line X) and humoral Immunity (line Y). First (above) and second (below) pair of canonical roots

Discussion of the results we will carry out in the following article together with data on neural regulation of cellular immunity.

ACKNOWLEDGMENT

We express our sincere gratitude to administration JSC “Truskavets’kurort” for help in carrying out immune tests and recording EEG and HRV.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

For all authors any conflict of interests is absent.

REFERENCES

1. Baevskiy RM, Ivanov GG. Heart Rate Variability: theoretical aspects and possibilities of clinical application [in Russian]. *Ultrazvukovaya i funktsionalnaya diagnostika*. 2001; 3: 106-127.
2. Berntson GG, Bigger JT jr, Eckberg DL, Grossman P, Kaufman PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van der Molen MW. Heart Rate Variability: Origines, methods, and interpretive caveats. *Psychophysiology*. 1997; 34: 623-648.
3. Heart Rate Variability. Standards of Measurement, Physiological Interpretation, and Clinical Use. Task Force of ESC and NASPE. *Circulation*. 1996; 93(5): 1043-1065.
4. Khaspekova NB. Diagnostic informativeness of monitoring HRV [in Russian]. *Vestnik aritmologii*. 2003. 32: 15-23.
5. Khayutin VM, Lukoshkova EV. Spectral analysis of the heart rate oscillations: physiological foundation and complicating it phenomena [in Russian]. *Russian Journal of Physiology*. 1999; 85(7): 893-909.
6. Korkushko OV, Pysaruk AV, Shatylo VB. The value of heart rate variability analysis in cardiology: age aspects [in Russian]. *Circulation and Hemostase*. 2009; 1-2: 127-139.
7. Kotelnikov SA, Nozdrachov AD, Odinak MM, Shustov EB, Kovalenko IYu, Davidenko VYu. Heart rate variability: understanding of the mechanisms [in Russian]. *Fiziologiya cheloveka*. 2002; 28(1): 130-143.
8. Kozyavkina OV. Vegetotropic effects of bioactive water Naftyssya at children with dysfunction of the neuroendocrine-immune complex, these endocrine-immune accompaniment and the ability to predict [in Ukrainian]. *Medical Hydrology and Rehabilitation*. 2011; 9(2): 24-39.
9. Kozyavkina OV. Vegetotropic effects of bioactive water Naftyssya at males rats and their endocrine, electrolyte and immune accompaniments [in Ukrainian]. *Medical Hydrology and Rehabilitation*. 2012; 10(3): 65-92.
10. Kozyavkina OV, Kozyavkina NV, Gozhenko OA, Gozhenko AI, Barylyak LG, Popovych IL. Bioactive Water Naftussya and Neuroendocrine-Immune Complex [in Ukrainian]. Kyiv: UNESCO-SOCIO. 2015. 349 p.
11. Kozyavkina OV, Popovych IL, Zukow W. Immediate vegetotropic effects of bioactive water Naftussya and their neuro-endocrine-immune accompaniment in healthy men. *Journal of Health Sciences*. 2013; 3(5): 391-408.
12. Kul’chyns’kyi AB. The relationships between changes in parameters of Electroencephalogram and Immunogram in the conditions balneotherapy on spa Truskavets’ [in Ukrainian]. In: *Valeology: current status, trends and perspectives of development*. Abstracts. XIV Intern. scient. and practical.

- conf. (Kharkiv-Drohobych, 14-16 April 2016). Kharkiv: VN Karazin KhNU. 2016: 322-323.
13. Kul'chyns'kyi AB. Correlations between parameters EEG, HRV and phagocytosis at patients with chronic pyelonephrite and cholecystite. In: XVI International Conference "The current status and approaches to development of physical and rehabilitation medicine in Ukraine according to international standards" (15-16 December 2016, Kyiv). Kyiv, 2016: 163.
 14. Kul'chyns'kyi AB, Gozhenko AI, Zukow W, Popovych IL. Neuro-immune relationships at patients with chronic pyelonephritis and cholecystitis. Communication 3. Correlations between parameters EEG, HRV and Immunogram. Journal of Education, Health and Sport. 2017; 7(3): 53-71.
 15. Kul'chyns'kyi AB, Kovbasnyuk MM, Korolyshyn TA, Kyjenko VM, Zukow W, Popovych IL. Neuro-immune relationships at patients with chronic pyelonephrite and cholecystite. Communication 2. Correlations between parameters EEG, HRV and Phagocytosis. Journal of Education, Health and Sport. 2016; 6(10): 377-401.
 16. Kul'chyns'kyi AB, Kyjenko VM, Zukow W, Popovych IL. Causal neuro-immune relationships at patients with chronic pyelonephritis and cholecystitis. Correlations between parameters EEG, HRV and white blood cell count. Open Medicine. 2017; 12(1): 201-213.
 17. Lapovets' LYe, Lutsyk BD. Handbook of Laboratory Immunology [in Ukrainian]. L'viv. 2002. 173 p.
 18. Lukovych YuS, Popovych AI, Kovbasnyuk MM, Korolyshyn TA, Barylyak LG, Popovych IL. Neuroendocrine-immune support of diuretic effect of balneotherapy on Truskavets resort [in Ukrainian]. Kidneys. 2015; 2(12): 68-75.
 19. Nance DM, Sanders VM. Autonomic innervation and regulation of immune system (1987-2007). Brain Behav Immun. 2007; 21(6): 736-745.
 20. Newberg AB, Alavi A, Baime M, Pourdehnad M, Santanna J, d'Aquili E. The measurement of regional cerebral blood flow during the complex cognitive task of meditation: a preliminary SPECT study. Psychiatry Research: Neuroimaging Section. 2001; 106: 113-122.
 21. Popovych IL. The concept of neuro-endocrine-immune complex (review) [in Russian]. Medical Hydrology and Rehabilitation. 2009; 7(3): 9-18.
 22. Popovych IL. Stresslimiting Adaptogene Mechanism of Biological and Curative Activity of Water Naftussya [in Ukrainian]. Kyiv: Computerpress. 2011. 300 p.
 23. Popovych IL, Kozyavkina OV. Immediate vegetotropic effects of bioactive water Naftussya and their neuro-endocrine-immune accompaniment in healthy men [in Ukrainian]. Medical Hydrology and Rehabilitation. 2012; 10(3): 31-64.
 24. Popovych IL, Kul'chyns'kyi AB, Kovbasnyuk MM, Korolyshyn TA, Barylyak LG, Tkachuk SP. Neuro-immune relationships in patients with chronic pyelonephritis and cholecystitis in conditions for balneotherapy on spa Truskavets' [in Ukrainian]. In: Proceedings VIII Scientific Conference "Issues of pathology in conditions of extreme factors action on the body" (Ternopil', 1-2 October 2015). Ternopil'. 2015: 73-74.
 25. Popovych IL, Kul'chyns'kyi AB, Kovbasnyuk MM, Korolyshyn TA, Barylyak LG, Zukow W. Neuro-immune relationships and homunculus conception. In: Pathophysiology and Pharmacy: ways of integration: Abstracts VII National Congress pathophysiologists Ukraine with international participation (5-7 October 2016). Kharkiv: Publishing National Pharmaceutic University. 2016: 21.
 26. Popovych IL, Vis'tak (Markevych) HI, Humega MD, Ruzhylo SV. Vegetotropic Effects of Bioactive Water Naftussya and their Neuroendocrine-Immune, Metabolic and Hemodynamic Accompaniments [in Ukrainian]. Kyiv: UNESCO-SOCIO. 2014. 162 p.
 27. Romodanov AP (editor). Postradiation Encephalopathy. Experimental Researches and Clinical Observations [in Ukrainian and Russian]. Kyiv: USRI of Neurosurgery. 1993. 224 p.
 28. Thayer JF, Sternberg EM. Neural aspects of immunomodulation: Focus on the vagus nerve. Brain Behav Immun. 2010; 24(8): 1223-1228.
 29. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest. 2007; 117(2): 289-296.