Popovych Andriy I., Popovych Igor L., Popovych Dariya V., Ruzhylo Sofiya V., Żukow Xawery. Relationships between changes in the state of neuroendocrine regulation and immunity in patients of Truskavets' spa. Journal of Education, Health and Sport. 2021;11(6): 335-347. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2021.11.06.036
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.06.036
https://zenodo.org/record/6561497

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 21.05.2021. Revised: 03.06.2021. Accepted: 30.06.2021.

Relationships between changes in the state of neuroendocrine regulation and immunity in patients of Truskavets' spa

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Abstract

Background. Earlier we showed that the balneotherapeutic complex of Truskavets' spa have significant modulating effects on parameters of EEG&HRV and Immunity of patients with chronic pyelonephritis and cholecystitis in remission accompanied of neuroendocrine-immune complex dysfunction. Were detected the close relationships between EEG, HRV, endocrine and immune parameters as well as between changes in EEG&HRV and immune parameters under the influence of balneotherapy. The aim of this study was to analyze the relationships between changes in the state of neuroendocrine regulation and immunity of the same patients. **Materials and Methods**. The object of clinical-physiological observation were 22 men aged 23-70 years, who underwent rehabilitation treatment of chronic pyelonephritis and cholecystitis in remission in the Truskavets' spa. The examination was performed twice, before and after a 9-11-day course of balneotherapy. The subject of the study were the parameters of the electroencephalogram, heart rate variability, hormones and immunity. **Results**. The method of canonical correlation analysis states that the changes in immunity caused by balneotherapy are determined by the constellation of alaptation hormones by 98,9%, the autonomic nervous system by 99,9%, the central nervous system by 99,7%. **Conclusion**. Immunomodulatory effect of balneotherapy is realized through the neuro-endocrine mechanism.

Keywords: Truskavets' spa, EEG, HRV, hormonal and immune parameters, relationships.

INRODUCTION

Earlier we showed that the balneotherapeutic complex of Truskavets' spa have significant modulating effects on parameters of EEG&HRV and Immunity of patients with chronic pyelonephritis and cholecystitis in remission accompanied of neuroendocrine-immune complex dysfunction [5,13,18,19]. In line with the concept of neuro-endocrine-immune complex [21], were detected the close relationships between EEG, HRV, endocrine and immune parameters in humans [10-12,23,26] and (without EEG) in rats [7,16,17,20,22], as well as between individual changes in EEG&HRV and immune parameters under the influence of balneotherapy [7,14,24,25]. The aim of this study was to analyze the relationships between individual changes in the state of neuroendocrine regulation and immunity of the same patients.

MATERIALS AND METHODS

The object of clinical-physiological observation were 22 men aged 23-70 years, who underwent rehabilitation treatment in the Truskavets' spa of chronic pyelonephritis and cholecystitis in remission with of neuroendocrine-immune complex dysfunction. The examination was performed twice, before and after a 9-11-day course of balneotherapy. Patients received standard balneotherapeutic complex: bioactive water Naftussya (3 ml/kg one hour before meals three times a day) and in half an hour additionally drank water "Mariya" in the same dose as well as application of Ozokerite on the lumbar region (temperature 45^0C, exposure 30 minutes, every other day, 5 procedures) and baths with mineral water (Cl^--SO_4^{2-}-Na^+-Mg^{2+} containing salt concentration 25 g/L, temperature 36-37^0C, duration 8-10 minutes, every other day, 5 procedures).

The day before, daily urine was collected, in which was determined the concentration of calcium (by reaction with arsenase III) and phosphates (phosphate-molybdate method). The same electrolithes were determined in plasma.

The analysis carried out according to instructions [6] with the use of analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

According to the parameters of Ca and phosphates exchange, parathyroid activity (PTA) was evaluated by coefficient $(Cap \bullet Pu/Cau \bullet Pp)^{0,25}$, based on its classical effects and recommendations by IL Popovych [7].

We determined content in plasma major hormones of adaptation: Cortisol, Testosterone, Calcitonin and Triiodothyronine (by the ELISA with the use of analyzer "RT-2100C" and corresponding sets of reagents from "Алкор Био", XEMA Co., Ltd and DRG International Inc.).

In basal conditions we estimated the state of the autonomous regulation by the method heart rate variability (HRV) [1,3,8,29], using a hardware-programmatic complex "CardioLab+HRV" (KhAI Medica, Kharkiv, Ukraine). The following parameters were subject to analysis. Frequency Domain Methods: HF (0,40÷0,15 Hz), LF (0,15÷0,04 Hz), VLF (0,04÷0,015 Hz), ULF (0,015÷0,003 Hz) bands. Time Domain Methods: HR, SDNN, RMSSD, pNN_{50}. Calculated CE Shannon's [29] Entropy (h) of the relative spectral powers (SP) of the HRV bands by IL Popovych's [28] formula:

$$hHRV=- [SPHF \bullet \log_2 SPHF + SPLF \bullet \log_2 SPLF + SPVLF \bullet \log_2 SPVLF + SPULF \bullet \log_2 SPULF]/\log_2 4$$

Simultaneosly with HRV we recorded EEG a hardware-software complex "NeuroCom Standard" (KhAI MEDICA, Kharkiv) 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. The duration of the epoch was 25 sec. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz) as well as absolute (μV^2/Hz) and relative (%) power spectrum density (PSD) 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.

We calculated also for each locus EEG CE Shannon's entropy (h) of normalized PSD using IL Popovych's [28] formula:

$$hEEG = - [PSD\alpha \bullet \log_2 PSD\alpha + PSD\beta \bullet \log_2 PSD\beta + PSD\theta \bullet \log_2 PSD\theta + PSD\delta \bullet \log_2 PSD\delta]/\log_2 4$$

Immune status evaluated as described in the manual [15]. 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 CD56 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. 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) as well as C-reactive protein (by the ELISA with the use of analyzer "RT-2100C"), Interleukins 1β and 6 (ELISA, analyzer "Stat Fax 303", USA, reagents from "Vector-Best", RF).

In portion of capillary the blood we counted up Leukocytogram and calculated the Entropy (h) of Leukocytogram (LCG) as well as Immunocytogram (ICG) using IL Popovych's [10] formulas:

$$hLCG = - [L \bullet \log_2 L + M \bullet \log_2 M + E \bullet \log_2 E + SNN \bullet \log_2 SNN + StubN \bullet \log_2 StubN]/\log_2 5$$

$$hICG = - [CD4 \bullet \log_2 CD4 + CD8 \bullet \log_2 CD8 + CD22 \bullet \log_2 CD22 + CD56 \bullet \log_2 CD56]/\log_2 4$$

Parameters of phagocytic function of neutrophils estimated as described by SD Douglas and PG Quie [4] with moderately modification by MM Kovbasnyuk [11]. The objects of phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index PhI), intensity (number of microbes absorbed one phagocytes - Microbial Count MC or Right's Index) and completeness (percentage of dead microbes - Killing Index KI). Based on the obtained parameters and the content of neutrophils in the blood, their bactericidal ability was calculated.

For statistical analysis used the software package "Statistica 64".

RESULTS AND DISCUSSION

At the first stage, the correlations between individual changes in hormone levels, on the one hand, and immunity parameters, on the other, were screened. Given the significant number of registered parameters of Immunity (n=25), for further analysis were purposefully selected only those which are subject to the **significant** modulating effect of Hormones (Table 1).

Table 1. Matrix of correlations between changes in hormone levels and immune parameters

Variable	Correlations N=22					
	PTA	Ald	T3	Cor	CT	Test
Ph I A	0,11	0,20	-0,43	-0,21	0,08	0,15
KI A	-0,15	-0,22	-0,01	-0,25	-0,62	0,07
Ph I E	0,02	-0,01	-0,44	-0,37	0,05	0,08
MC E	0,01	-0,02	-0,20	-0,04	0,57	-0,19
KI E	-0,26	-0,04	0,24	0,02	-0,73	0,02
H LCG	0,41	-0,36	-0,43	-0,50	0,17	0,11
BC A	0,20	-0,18	-0,14	-0,74	-0,18	0,09
BC E	0,07	-0,15	-0,23	-0,63	-0,17	0,07
Leuk	0,29	-0,34	-0,44	-0,88	-0,03	0,18
Mon	0,18	0,00	-0,09	-0,59	-0,15	0,05
Lymph	-0,20	-0,26	-0,13	0,49	0,18	-0,04
CD4	-0,10	-0,21	-0,02	0,38	0,25	0,01
CD22	-0,32	-0,20	0,46	0,23	-0,15	0,17
CIC	-0,23	-0,04	0,10	-0,08	-0,49	0,10
IgG	0,46	0,07	-0,09	-0,15	-0,13	-0,26
IgA	0,20	-0,01	-0,03	-0,14	-0,33	-0,14
IgM	0,14	-0,02	-0,34	-0,04	0,37	-0,10
O-Lym	0,33	0,26	-0,43	-0,30	0,09	-0,12
IL-1	-0,23	-0,09	0,13	0,34	0,13	0,33
IL-6	-0,42	-0,21	-0,05	0,43	0,33	-0,02

Note. According to the formula:

$|r| \geq \{exp[2t/(n-1,5)^{0,5}] - 1\}/\{exp[2t/(n-1,5)^{0,5}] + 1\}$,

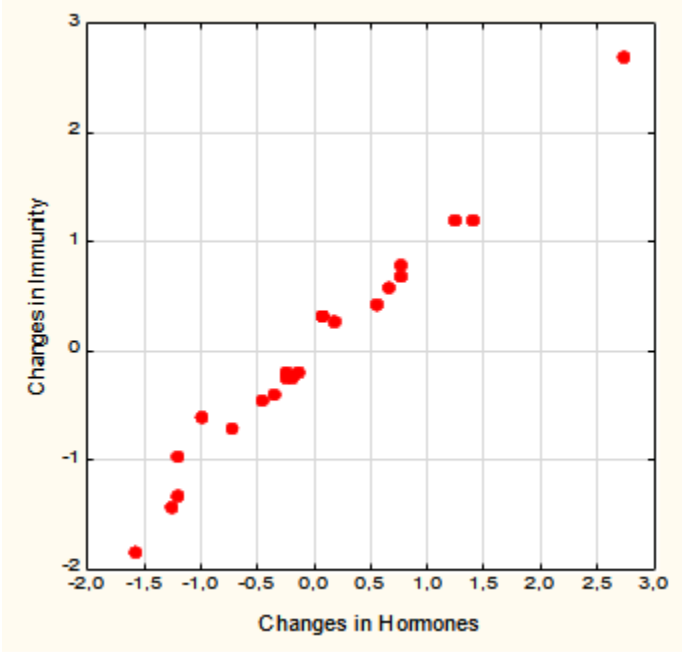
for a sample of 22 observations critical value of correlation coefficient module at p<**0,05** (t>2,09) is 0,43, at p<**0,02** (t>2,53) is 0,51, at p<**0,01** (t>2,84) is 0,56, at p<**0,001** (t>3,85) is 0,69.

In the second stage, the analysis of the canonical correlation between endocrine and immune sets of variables was performed. The maximum factor load on the endocrine root is given by changes in cortisol, which confirms its reputation as a major immunomodulator, while the aldosterone load is minimal (Table 2.).

Due to technical/mathematical limitations of the program, only 20 parameters can be used in the analysis, ie 2 less than the number of patients. Therefore, only 14 variables that are subject to **suppressive** or **enhancing** hormonal regulation fit into the root structure of immune changes. Judging by the coefficient of determination, hormonal reactions cause immunomodulation by 98,9% (Fig. 1).

Table 2. Factor structure of endocrine and immune canonical roots of changes

Endocrine Variables	R
Cortisol, nM/L	-0,750
Triiodothyronine, nM/L	-0,345
Aldosterone, pM/L	-0,075
Calcitonin, ng/L	0,451
Parathyroid Activity, units	0,277
Testosterone, nM/L	0,151
Immune Variables	**R**
Bactericidity vs Staph. aureus, Bact/L	0,548
Entropy of Leukocytogram	0,508
Monocytes, %	0,475
Bactericidity vs E. coli, Bacteria/L	0,453
Microbial Count vs E. coli, Bact/Phag	0,430
Immunoglobulins G, g/L	0,111
0-Lymphocytes, %	0,386
Killing Index vs E. coli, %	-0,547
$CD22^+$ B-Lymphocytes, %	-0,359
Circulating Immune Complexes, units	-0,288
Killing Index vs Staph. aureus, %	-0,280
Interleukin-6, ng/L	-0,255
Interleukin-1, ng/L	-0,251
$CD4^+$ T-helper Lymphocytes, %	-0,227



R=0,994; R^2=0,989; $\chi^2_{(84)}$=128; p=0,0012; Λ Prime<10^{-5}

Fig. 1. Scatterplot of canonical correlation between changes in Endocrine (X-line) and Immune (Y-line) parameters

Autonomic-immune relationships were analyzed by a similar algorithm (Tables 3 and 4).

Table 3. Matrix of correlations between changes in HRV and immune parameters

Variable	Correlations N=22						
	RMSSD	ULF	VLF	LF	HF	hHRV	LFnu
KI A	0,05	0,14	0,07	-0,08	0,15	0,42	-0,30
MC A	-0,10	-0,13	0,06	0,04	-0,26	-0,52	0,48
PhI E	-0,37	0,00	-0,32	-0,47	-0,43	-0,08	0,04
MC E	-0,24	-0,54	-0,26	-0,27	-0,42	-0,54	0,21
KI E	0,47	0,46	0,39	0,25	0,56	0,72	-0,44
PMNN	-0,18	-0,01	-0,08	0,24	-0,16	0,15	0,54
CD4	0,25	0,01	0,23	-0,04	0,10	-0,35	-0,20
CD8	-0,21	-0,38	-0,32	-0,21	-0,12	0,12	-0,02
CD22	0,39	0,27	0,43	0,38	0,49	0,01	-0,10
CIC	0,50	0,16	0,34	0,02	0,46	0,25	-0,36
IgA	-0,29	0,50	0,04	-0,09	-0,28	0,35	0,22
IgM	-0,16	-0,60	-0,33	-0,29	-0,33	-0,41	0,10
CD56	0,06	0,43	0,20	0,28	0,06	0,13	0,17
O-Lym	-0,40	-0,18	-0,40	-0,29	-0,45	0,08	0,16
IL-1	0,39	0,49	0,50	0,41	0,35	-0,08	-0,08
IL-6	0,41	0,15	0,32	0,07	0,15	-0,25	-0,15

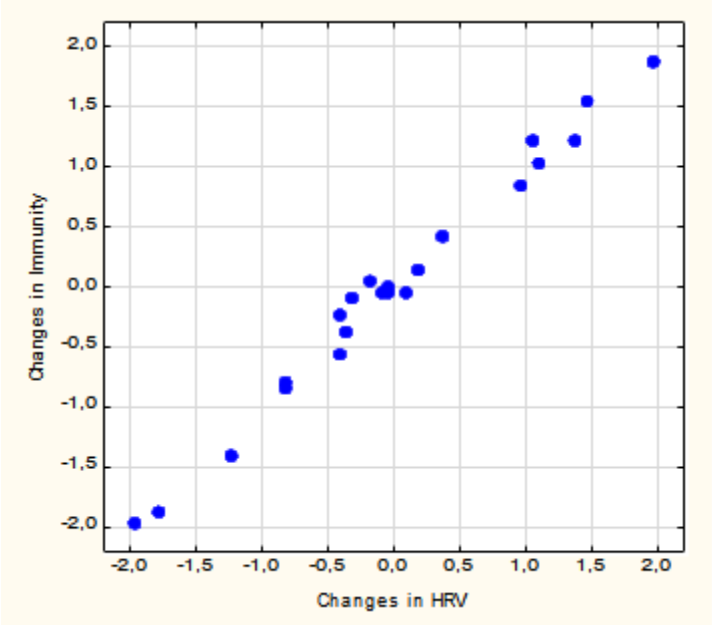
Table 4. Factor structure of HRV and immune canonical roots of changes

HRV Variables	**R**
LFnu, %	**-0,668**
Entropy of HRV	**0,781**
ULF band HRV, msec²	**0,673**
HF band HRV, msec²	**0,485**
VLF band HRV, msec²	**0,436**
LF band HRV, msec²	**0,166**
Immune Variables	**R**
Killing Index vs E. coli, %	**0,735**
Killing Index vs Staph. aureus, %	**0,396**
Circulating Immune Complexes, units	**0,368**
Immunoglobulins A, g/L	**0,264**
Interleukin-1, ng/L	**0,222**
$CD56^+$ NK-Lymphocytes, %	**0,184**
$CD22^+$ B-Lymphocytes, %	**0,085**
Microbial Count vs Staph. aur, Bac/Ph	**-0,503**
Microbial Count vs E. coli, Bacter/Phag	**-0,494**
Immunoglobulins M, g/L	**-0,415**
Polymorphonucleary Neutrophils, %	**-0,191**
$CD8^+$ T-cytolytic Lymphocytes, %	**-0,143**
Phagocytosis Index vs E. coli, %	**-0,083**
0-Lymphocytes, %	**-0,042**

The large factor load on the root of the autonomic response to balneotherapy by the HRV-marker of sympathetic tone (LFnu) confirms its important role in immunomodulation, along with the HRV-marker of vagal tone (HF). However, even more load is given by the ULF band. This is where it is appropriate to talk about the VLF and ULF bands, given their ambiguous interpretation. Because in our device ULF band (range 0,015÷0,003 Hz) is

integrated into the lower zone of VLF (0,04÷0,0033 Hz) band, in fact it is a component of the latter.

In an excellent review, F Shaffer and JP Ginsberg [30] said that there is uncertainty regarding the physiological mechanisms responsible for activity within the VLF band. The heart's intrinsic nervous system appears to contribute to the VLF rhythm and the sympathetic nervous system influences the amplitude and frequency of its oscillations. VLF power may also be generated by physical activity, thermoregulatory, renin–angiotensin, and endothelial influences on the heart. Vagal activity may contribute to VLF power since parasympathetic blockade almost completely abolishes it. In contrast, sympathetic blockade does not affect VLF power and VLF activity is seen in tetraplegics, whose sympathetic nervous system innervation of the heart and lungs is disrupted. Nevertheless, the maximum factor load is given by the entropy of HRV, the physiological essence of which is analyzed in detail in the just published monograph [7]. Judging by the coefficient of determination, autonomous reactions cause immunomodulation by 99,9% (Fig. 1).



R=0,9996; R^2=0,9993; $\chi^2_{(84)}$=145; p<10^{-4}; Λ Prime<10^{-6}

Fig. 2. Scatterplot of canonical correlation between changes in HRV (X-line) and Immune (Y-line) parameters

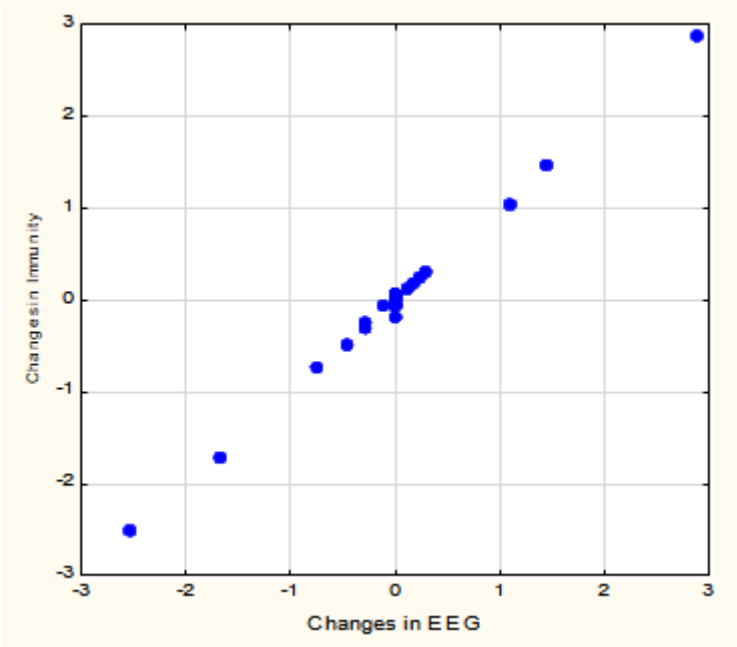
The CNS has a similar strength of immunomodulatory effect (Tables 5-6, Fig. 3).

Table 5. Matrix of correlations between changes in EEG and immune parameters

Roo	Correlations, left set with right s									
Vari	IL6	CF	IL1	HC	PN	E6	IgG	IgM	Cyt	HC
DD	0,5	0,5	0,2	−0,	−0,	0,0	−0,	0,0	−0,	0,
P2T	0,0	0,	−0	0,4	−0,	0,2	0,	0,4	0,2	0,0
HF7	0,4	0,0	−0	−0,	−0,	−0,	−0,	0,	−0,	0,2
FT%	0,5	0,0	0,0	0,0	−0,	0,0	−0,	0,	0,0	−0,
FD	−0,	−0	−0	0,2	−0,	0,	0,	0,	0,4	−0,
FA	−0,	0,	−0	0,4	−0,	0,4	0,2	0,	0,	0,
T4	0,0	0,	−0	0,3	−0,	0,2	0,	0,5	0,3	−0,
HT6	0,4	0,0	−0	−0,	−0,	−0,	−0,	0,	−0,	0,2
HD2	0,0	0,0	0,0	−0,	−0,	0,0	−0,	0,0	−0,	0,
OD2	−0,	−0	−0	0,4	0,0	0,	0,3	0,0	0,2	−0,

Table 6. Factor structure of EEG and Immune canonical roots of changes

EEG Variables	R
F8-α PSD, $\mu V^2/Hz$	0,432
O2-δ PSD, $\mu V^2/Hz$	0,335
Fp2-θ PSD, $\mu V^2/Hz$	0,118
Entropy F7	0,105
Entropy T6	0,043
F7-θ PSD, %	0,004
F7-δ PSD, $\mu V^2/Hz$	-0,466
Entropy O2	-0,138
Deviation δ, Hz	-0,129
T4-θ PSD, $\mu V^2/Hz$	-0,039
Immune Variables	**R**
Interleukin-6, ng/L	-0,319
Immunoglobulins M, g/L	-0,264
Interleukin-1, ng/L	-0,074
0-Lymphocytes, %	-0,305
Entropy of Immunocytogram	0,597
Immunoglobulins G, g/L	0,247
Entropy of Leukocytogram	0,212
Eosinophils, %	0,062
Polymorphonucleary Neutrophils, %	0,035
C-RP, mg/L	0,019



R=0,998; R^2=0,997; $\chi^2_{(100)}$=132; p=0,019; Λ Prime<10^{-5}

Fig. 3. Scatterplot of canonical correlation between changes in EEG (X-line) and Immune (Y-line) parameters

We want to draw attention to the real regulatory role of entropy in both the nervous and immune systems [7]. Because it is difficult for us to imagine how the CNS can directly perform immunomodulation, the mediating role of the endocrine and autonomic nervous systems seems more realistic.

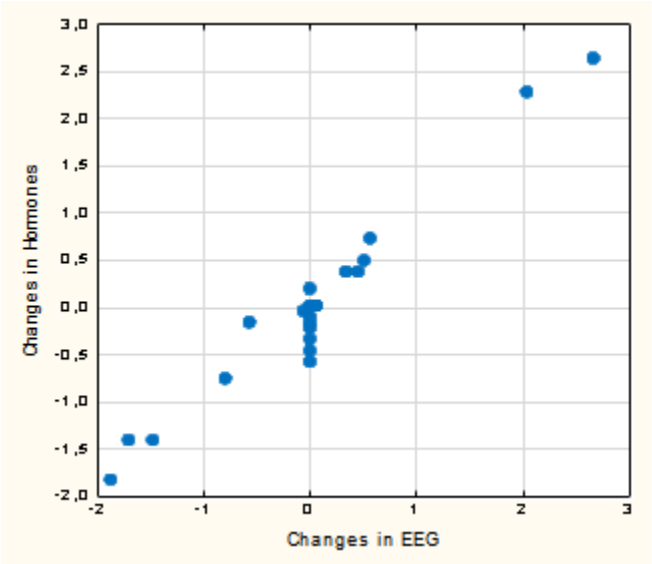
The results of canonical correlation analysis show a significant impact of the CNS on both the endocrine (Tables 7-8 and Fig. 4) and autonomic nervous (Tables 9-10 and Fig. 5) systems, the immunomodulatory effect of which is well known and documented in this study.

Table 7. Matrix of correlations between changes in EEG and Endocrine parameters

Root	Correlations, left set with right se					
Variable	PTA	Ald	T3	Cor	CT	Test
DD	-0,7	0,0(	0,07	0,3ε	0,2⁴	0,04
Fp2T	0,0ε	-0,3	-0,1ϑ	-0,1(	-0,0	-0,2ϑ
F7H	-0,5	0,01	0,25	0,4C	0,3⁴	-0,3
F7T%	-0,4(	-0,1	-0,1(	0,2ε	0,3⁴	-0,0ϑ
F7D	0,44	-0,1	-0,3ε	-0,2·	-0,3	0,13
F8D%	0,77	-0,1	-0,1ε	-0,1ϑ	-0,0	-0,0ε
F8A	0,2(	-0,3	-0,3ϑ	-0,2(	0,21	-0,0ϑ
T4B%	-0,4·	0,0ϑ	0,11	0,44	0,2⁴	0,23
T4T	0,0ε	-0,2·	-0,2(	-0,1ε	0,0ε	-0,3ε
T6H	-0,6(	0,0ϑ	0,29	0,3ϑ	0,1⁴	-0,3(
O2H	-0,5(	-0,0	0,23	0,47	-0,0	-0,3⁴
O2D	0,7ϑ	-0,2	-0,2ε	-0,5	-0,1·	0,02

Table 8. Factor structure of EEG and Endocrine canonical roots of changes

EEG Variables	R
T4-β PSD, %	0,491
Entropy F7	0,476
Deviation δ, Hz	0,470
F7-θ PSD, %	0,413
Entropy T6	0,300
Entropy O2	0,186
F7-δ PSD, $\mu V^2/Hz$	-0,459
O2-δ PSD, $\mu V^2/Hz$	-0,443
F8-δ PSD, %	-0,290
Fp2-θ PSD, $\mu V^2/Hz$	-0,149
T4-θ PSD, $\mu V^2/Hz$	-0,113
Endocrine Variables	**R**
Calcitonin, ng/L	0,861
Cortisol, nM/L	0,501
Testosterone, nM/L	0,210
Triiodothyronine, nM/L	0,022
Parathyroid Activity, units	-0,390
Aldosterone, pM/L	-0,073



R=0,972; R^2=0,946; $\chi^2_{(66)}$=85; p=0,058; Λ Prime=0,0008

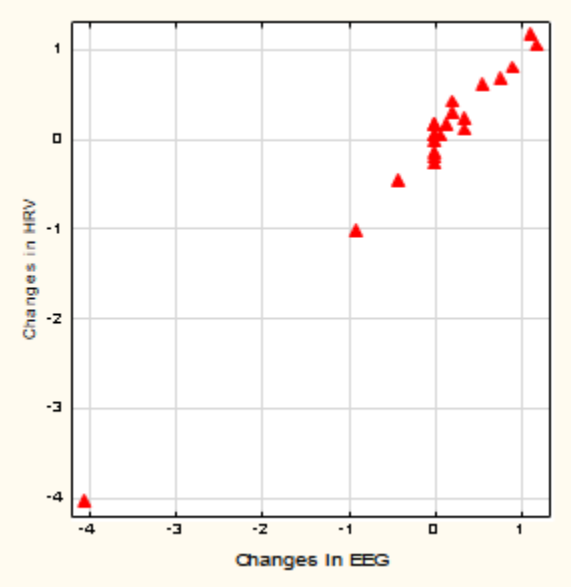
Fig. 4. Scatterplot of canonical correlation between changes in EEG (X-line) and Endocrine (Y-line) parameters

Table 9. Matrix of correlations between changes in EEG and HRV parameter

Root	Correlations, left set with right s					
Variabl	RMS:	ULF	VLF	LF	HHF	LFnu
DD	0,2	0,1	0,3	0,C	-0,2	-0,C
Fp2T	0,C	-0,5	-0,3	-0,3	0,C	-0,4
F7H	0,1	-0,3	-0,1	-0,1	-0,3	0,C
F7T%	0,2	-0,2	-0,1	-0,2	-0,1	-0,2
F7D	0,C	0,C	0,1	0,C	0,3	-0,2
F8A	-0,1	-0,1	-0,4	-0,2	0,1	-0,2
T4B%	-0,C	0,4	0,2	0,C	-0,1	0,1
T4T	0,C	-0,6	-0,4	-0,3	-0,C	-0,3
T6H	0,2	-0,2	-0,C	-0,1	-0,2	-0,C
O2H	0,2	0,C	0,C	-0,C	-0,C	-0,1
O2D	-0,3	-0,1	-0,3	-0,1	0,1	-0,C

Table 10. Factor structure of EEG and HRV canonical roots of changes

EEG Variables	R
T4-θ PSD, $\mu V^2/Hz$	0,869
Fp2-θ PSD, $\mu V^2/Hz$	0,806
F7-θ PSD, %	0,458
F8-α PSD, $\mu V^2/Hz$	0,248
Entropy T6	0,357
Entropy F7	0,334
Entropy O2	0,126
T4-β PSD, %	-0,476
HRV Variables	**R**
ULF band HRV, $msec^2$	-0,885
VLF band HRV, $msec^2$	-0,412
LF band HRV, $msec^2$	-0,425
Entropy of HRV	-0,341
LFnu, %	-0,223



R=0,992; R^2=0,985; $\chi^2_{(77)}$=130; p=0,0001; Λ Prime=0,00001
Fig. 5. Scatterplot of canonical correlation between changes in EEG (X-line) and HRV (Y-line) parameters

CONCLUSION

It is traditionally believed that loci T3/T4 reflect the activity of the amygdala [27]. In practice, transcranial magnetic and direct current stimulation of the T3/T4 scalp position is used to reach the insular cortex [review: 2,9]. The figures presented by Winkelmann T et al [31] and Yoo HJ et al [32] give us reason to assume that the loci T3/T4 projected inferior temporal gyrus. These cortical structures affect the activity of the vagus and sympathetic nuclei.

It seems that these structures of the CNS play a major role in the impact of balneotherapy on the autonomic nervous, endocrine and immune systems of the body.

ACKNOWLEDGMENT

We express sincere gratitude to VV Kikhtan as well as administration of clinical sanatorium “Moldova” for help in recording tests.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out 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.

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