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Similarity effects of two types of adaptogens (transcutaneous electrical stimulation with the device "VEB" ® and using of bioactive Naftussya water) on the human body

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Abstract

Background. The studies of the Truskavetsian Scientific School of Balneology have shown that both the Naftussya bioactive water and the standard balneotherapy complex (Naftussya drink, ozokerite applications, mineral baths) exhibit the properties of adaptogens, similar to such ginseng and phytocompositions. At the same time, in the process of researching the influence of devices for transcutaneous electrical stimulation on the human body, we found that changes in the parameters of the neuro-endocrine-immune complex and metabolism also have an adaptogenic character. The purpose of this study is to find effects common to adaptogens of chemical and physical nature. **Materials and Methods**. The object of observation were 29 women 30-76 (50±13) y and 28 men 25-69 (48±13) y without a clinical diagnosis, but with the deviations from the norm in a number of parameters of the neuro-endocrine-immune complex as a manifestation of dysadaptation. Parameters of biophotonics, acupuncture points, EEG, HRV, immunity, metabolism, blood pressure and hormones levels before and after a four-day transcutaneous electrical stimulation session or one-week course of drinking of Naftussya water registered. **Results.** Screening revealed that 43 variables respond to the action of adaptogens according to the law of the initial level, at the same time, 4 initially elevated and 9 normal variables show further growth. Caused by adaptogens changes in 7 EEG and 7 HRV parameters determine favorable changes in 2 endocrine, 10 immune, 3 metabolic, 2 hemodynamic and 3 biophotonics parameters by 83,5%. **Conclusion**. The adaptogens both of chemical and physical nature, activating the receptors of the gut mucosa or the skin, respectively, have similar favorable effects on the parameters of the neuroendocrine-immune complex, metabolism, hemodynamics and biophotonics.

Keywords: transcutaneous electrical stimulation, bioactive Naftussya water, neuroendocrine-immune complex, metabolism, hemodynamics, biophotonics.

INTRODUCTION

Since the landmark discovery of Selye H [1936] it is known that the nonspecific pathogenetic basis of many chronic diseases is stress (general adaptation syndrome). This concept is developed by its many followers [Horizontov PD et al., 1983; Meerson FZ, 1986; 1993; Garkavi LKh et al., 1990; 1998; 2000; Kolyada TI et al., 1995; Chrousos GP, 1998; 2000; Radchenko OM, 2004; Reznikov OG et al., 2004; Baraboy VA, Reznikov OG, 2013; Popovych IL, 2011; Dhabhar FS, 2018; Reznikov OG, 2019; Dhabhar FS, 2018; Popovych IL et al, 2020].

The physiological antipode of stressors are adaptogens that have a stress-limiting effect by inducing anti-stress (eustress) general adaptation reactions. The level of resistance of the organism is determined by the quality of its general adaptation reaction [Garkavi LKh et al., 1990; Popovych IL et al., 2000]. By Garkavy LKh et al. [1990], adaptogens should be considered ***all stimuli and influences*** (electric stimulation of the hypothalamus, carbon dioxide as an irritant of the reticular formation and interoreceptors, magnetic fields, neurotropic agents, immunomodulators, antioxidants, muscle strain, biostimulants of plant and animal origin) that, when exposed to the body, can cause a ***particular general adaptive reaction***. However, most authors to adaptogens include only ***substances*** that can cause a state of "***nonspecific increased resistance***" [Lazarev NV, 1960] of the body to the effects of adverse environmental factors of physical, chemical and biological nature [Brekhman II, 1968; Dardymov IV, 1976; Saratikov AS & Krasnov YA, 1987; Kaplan EA et al., 1990; Yakovlev GM et al., 1990; Panossian AG et al., 2022]. Another hypostasis of the adaptogenic action of the means is their regulatory effect, that is, the normalization of the deviated parameters of the body, regardless of their orientation [Dardymov IV, 1976; Saratikov AS & Krasnov YA, 1987]. Panossian AG et al. [2022] gave the following definition in a recent excellent review. ***Adaptogens comprise a category of herbal medicinal and nutritional products promoting adaptability, resilience, and survival of living organisms in stress.*** Adaptogens have pharmacologically pleiotropic effects on the neuroendocrine-immune system, which explain their traditional use for the treatment of a wide range of conditions. They exhibit a biphasic dose-effect response: at low doses they function as ***mild stress-mimetics, which activate the adaptive stress-response signaling pathways to cope with severe stress***. That is in line with their traditional use for preventing premature aging and to maintain good health and vitality.

Long-term and numerous experimental and clinical studies of the Truskavetsian Scientific School of Balneology have shown that both the Naftussya bioactive water used as monotherapy and the standard balneotherapy complex (Naftussya drink, ozokerite applications, mineral baths) exhibit the described properties of adaptogens, similar to such ginseng and phytocompositions [Yaremenko MS et al., 1989; Aleksyeyev OI et al., 1996; Ivassivka SV, 1997; Ivassivka SV et al., 1999; Popovych IL et al., 2003; 2014; Kostyuk PG et al., 2006; Kozyavkina OV et al., 2015; Dranovs'kyi AL & Popovych IL, 2010; Popovych IL, 2011; Popovych AI, 2018; 2019; 2022; Gozhenko AI et al., 2021]. If we accept the position that the organic substances of Naftussya water, ozokerite, and oil (**naphta** in Greek) have a common origin [Yessypenko BY, 1981; Yaremenko MS et al., 1989; Ivassivka SV, 1997], on the one hand, and oil arose as a result of the metamorphism of the remains of phyto- and zooplankton, which were buried in layers of sedimentary rocks, on the other hand, then Naftussya water and ozokerite, in principle, it can also be attributed to **phytoadaptogens**. By the way, an additional source of organic substances in Naftussya water is fallen leaves on the surface of the deposit [Ivassivka SV et al., 1994].

At the same time, in the process of researching the influence of devices for transcutaneous electrical stimulation on the human body, we found that changes in the parameters of the neuro-endocrine-immune complex and metabolism also have an adaptogenic character [Babelyuk VY et al., 2018; 2022; Babelyuk NV et al., 2018]. So, the authors of the concept of anti-stressor general adaptation reactions were right!

The purpose of this study is to find effects on the parameters of the neuro-endocrine-immune complex and metabolism common to adaptogens of a chemical (oil/vegetable) and physical (physiotherapeutic) nature.

MATERIAL AND RESEARCH METHODS

The object of observation were employees of the clinical sanatorium "Moldova" and PrJSC "Truskavets' Spa": 29 women 30-76 (50±13) y and 28 men 25-69 (48±13) y. The volunteers were considered practically healthy (without a clinical diagnosis), but the initial testing revealed deviations from the norm in a number of parameters of the neuro-endocrine-immune complex (details follow) as a manifestation of dysadaptation, which actually prompted them to participate in the study with the hope of recovery.

In the morning in basal condition registered kirlianogram by the method of GDV by the device of "GDV Chamber" ("Biotechprogress", SPb, RF). Method of GDV, essence of which consists in registration of photoelectronic emission of skin, induced by high-frequency electromagnetic impulses, allows to estimate integrated psycho-somatic state of organism. The first base parameter of GDV is area of gas discharge image (GDI) in Right, Frontal and Left projections registered both with and without polyethylene filter. The second base parameter is a coefficient of shape (ratio of square of length of external contour of GDI toward his area), which characterizes the measure of serration/fractality of external contour. The third base parameter of GDI is entropy, id est measure of chaos. It is considered that GDI, taken off without filter, characterizes the functional changes of organism, and with a filter characterizes organic changes. Program estimates also Energy and Asymmetry of virtual Chakras [Korotkov KG, 2001; 2007; 2014].

Then recorded simultaneosly electrocardiogram (ECG) and electroencephalogram (EEG). ECG recorded during 7 min in II lead to assess the parameters of heart rate variability (HRV) (hardware-software complex "CardioLab+HRV" produced by "KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Temporal parameters (Time Domain Methods): heart rate (HR), mode (Mo), the standart deviation of all NN intervals (SDNN), 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 (pNN_{50}), triangular index (TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV: high-frequency (HF, range 0,40÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,040÷0,015 Hz) and ultra low-frequency (ULF, range 0,015÷0,003 Hz) [HRV, 1996; Berntson GG et al., 1997]. Calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (CI)=(VLF+LF)/HF), Baevskiy's Stress Index and Activity Regulatory Systems Index (BARSI) [Baevskiy RM & Ivanov GG, 2001].

EEG recorded during 25 sec 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 on the earlobes. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute (μV^2/Hz) and relative (%) 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. In addition, calculated coefficient of Asymmetry (As) and Laterality Index (LI) for PSD each Rhythm using formulas [Newberg AB et al., 2001]:

As, % = 100•(Max – Min)/Min; LI, % = Σ [200•(Right – Left)/(Right + Left)]/8.

We calculated for HRV and each locus EEG the Entropy (h) of normalized PSD using Popovych's IL [Gozhenko AI et al., 2021] formulas based on classic Shannon's CE [1948] formulas:

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

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

Next object of the study was blood pressure (BP). Systolic (Ps) and diastolic (Pd) BP (as well as simultaneously HR) was measured (by tonometer "Omron M4-I", Netherlands) in a sitting position three times in a row with calculation BP2/BP1 and BP3/BP1 indexes [Kozyavkina NV et al., 2020; 2020a]. The Kerdö's Vegetative Index [Kerdö I, 1966; Fajda OI et al., 2015] as marker of Sympathetic/Vagal balance calculated by formula: 100•(1-BPd/HR).

Electroconductivity (EC) recorded in follow points of acupuncture: Pg(ND), TR(X) and MC(AVL) at Right and Left side. Used complex "Medissa". For each pair, the Laterality Index was calculated according to the already mentioned formula.

Next determined the Elektrokinetic Index (EKI) as rate of electronegative nuclei of buccal epithelium by intracellular microelectrophoresis on the device "Biotest" (Kharkiv University), according to the method described [Kyrylenko IG et al., 2016; 2018; 2018a].

In portion of capillary blood counted up Leukocytogram (LCG) (Eosinophils, Stub and Segmentonucleary Neutrophils, Lymphocytes and Monocytes) and calculated its Adaptation Index as well as Strain Index by Popovych IL [2000].

The informativeness of these indices was demonstrated by other authors [Hubyts'kyi VY et al., 2013], as well as its advantage over the Lymphocytes/Segmentonucleary Neutrophils ratio [Garkavi LKh et al., 2000].

We remind that the algorithm of quantization of the Popovych's indexes is based on the proposed Garkavi LKh et al [1990; 1998] ranges of relative content in the leukocytogram of lymphocytes, which determines the type of General Adaptation Reaction of Organism as well as other components of leukocytogram and total leukocyte levels indicating harmonic or disharmonious character of GARO (Table 1).

Table 1. Quantification of General Adaptation Reaction of Organism, first version []

Leukocyto-gram Lymphocy-tes level, %	**G**eneral **A**daptation **R**eaction of **O**rganism	Eosinophils and Stub Neutrophils: 1÷6 %; Monocytes: 4÷7 %; Leukocytes: 4÷8 G/l	Eosinophils and Stub Neutrophils: <1; >6; Monocytes: <4; >7; Leukocytes: <4; >8 G/l
<21	Stress	**1,22**	**0,02**
21÷27	Training	**1,46**	**0,74**
28÷33	Quiet Activation	**1,95**	**0,98**
34÷43,5	Heightened Activation	**1,70**	**0,50**
≥44	Superactivation	**0,26**	

Strain Index-1 = $[(Eo/3{,}5\text{-}1)^2 + (SN/3{,}5\text{-}1)^2 + (Mon/5{,}5\text{-}1)^2 + (Leu/6\text{-}1)^2]/4$.

Later, Garkavi LKh et al [2000] proposed some other boundaries of ranges, on the basis of which we calculated the second version of the indices (Table 2).

Table 2. Quantification of General Adaptation Reaction of Organism, second version []

Leukocyto-gram Lymphocy-tes level, %	**G**eneral **A**daptation **R**eaction of **O**rganism	Eosinophils: 1÷4,5 %; Stub Neutrophils: 3÷5,5 %; Monocytes: 5÷7 %; Leukocytes: 4÷6 G/l	Eosinophils: <1;>4,5% Stub Neutrophils: <3; >5,5; Monocytes: <5; >7; Leukocytes: <4; >6 G/l
<21	Stress	**1,22**	**0,02**
21÷27	Training	**1,46**	**0,74**
28÷33	Quiet Activation	**1,95**	**0,98**
34÷43,5	Heightened Activation	**1,70**	**0,50**
≥44	Superactivation	**0,26**	

Strain Index-2 = $[(Eo/2{,}75\text{-}1)^2 + (SN/4{,}25\text{-}1)^2 + (Mon/6\text{-}1)^2 + (Leu/5\text{-}1)^2]/4$.

Parameters of phagocytic function of neutrophils estimated as described by Douglas SD and Quie PG [1981] with moderately modification by Kovbasnyuk MM [Kul'chyns'kyi AB et al., 2016]. 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). On the basis of the registered partial parameters of phagocytosis, taking into account the content of neutrophils (N) in 1 L of blood, the integral parameter - the bactericidal capacity of neutrophils - was calculated by the formula:

BCCN (10^9 Bact/L) = N (10^9/L)•PhI (%)•MC (Bact/Phag)•KI (%)•10^{-4}.

For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD25, 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) [Lapovets' LYe & Lutsyk BD, 2004].

We calculated also the Entropy of Immunocytogram (ICG) and Leukocytogram (LCG) using Popovych's formulas [Popovych IL, 2011]:

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

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

At last in portion of venous blood determined plasma levels of major hormones of adaptation: Cortisol, Testosterone, Aldosterone, Triiodothyronine and Calcitonin (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.); proinflammatory mediators: IL-1, IL-6 and C-reactive protein (ELISA, analyzer "RT-2100C", reagents from "Vector-Best"), as well as routine biochemical parameters: total cholesterol (by a direct method after the classic reaction by Zlatkis-Zack) and content of him in composition of high-density lipoproteins (by the enzyme method), direct and free bilirubin, asparagine and alanine transaminase according to instructions [Goryachkovskiy AM, 1998] with the use of analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

After the initial testing, an transcutaneous electrical stimulation session performed (four days) with the "VEB-1"® (7 women and 14 men) or the "VEB-2" (12 women and 5 men) devices [Babelyuk VY et al., 2017; 2020] or course of drinking of Naftussya water (seven days, 10 women and 9 men) carried out. The next morning after completing the treatment, retesting was performed.

Reference values are taken from the database of our laboratory (EEG, GDV, Immunity) or instructions (HRV, ELISA, biochemical tests). Results processed using the software package "Statistica 64".

RESULTS AND DISCUSSION

According to designed by your humble servant the algorithm of the Truskavetsian Scientific School, to enable a correct comparison of parameters expressed in different units and with different variability, which determines the "physiological price" of parameter changes, registered parameters-variables (V) were transformed into Z-score by the formula:

Z = (V-N)/SD = (V/N-1)/Cv, where

N is average norm, SD is standard deviation, Cv is coefficient of variation in norm.

At the next stage, two profiles of variables were created, the Z-scores of which before and after treatment (**regardless** of the nature of the means) differed significantly according to the Student's t test (Figs 1 and 2). In addition, several variables are present in the profiles, which, as a result of the following discriminant analysis, were included in the model despite their p-level>0,05. By the way, p-levels for pairwise comparisons and direct differences did not always coincide.

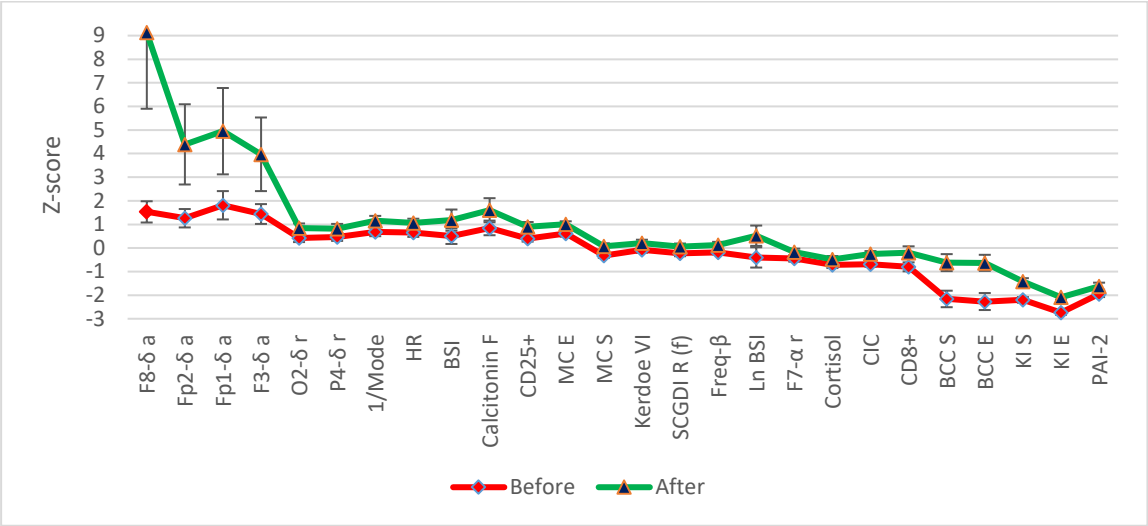


Fig. 1. Profiles of parameters whose levels (Z±SE) increased under the influence of adaptogens

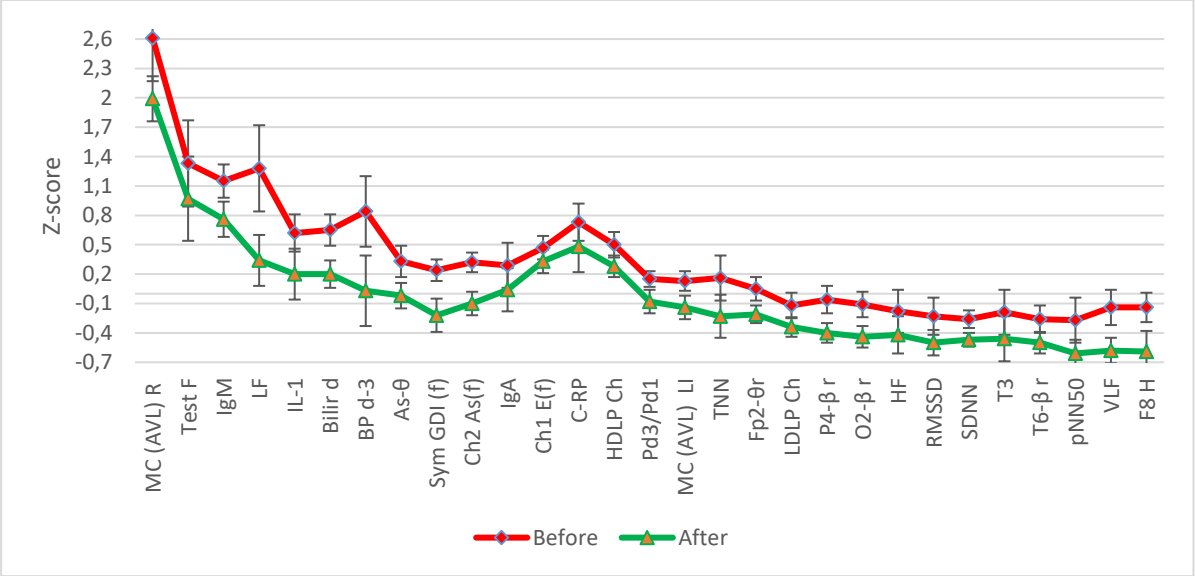


Fig. 2. Profiles of parameters whose levels (Z±SE) decreased under the influence of adaptogens

Then, based on the profiles, 7 quantitative-qualitative clusters were created (Fig. 3). Accepting the ±σ range as the norm, we state that the first cluster reflects a drastic upregulating effect of adaptogens on the initially moderately elevated 4 variables (see Table 21 for a list of variables). The second cluster reflects the further increase of the levels of 9 variables to the upper limit of the norm, the third - the complete normalization of the lower limit levels of 9 variables, the fourth - the minimization, but without normalization, of the degree of suppression of the other 5 variables. The remaining three clusters reflect the downregulating effects of adaptogens. In particular, a decrease to the upper limit of the norm of 4 variables, a complete

normalization of the upper limit levels of 10 variables, and a slight but statistically significant decrease of the initially normal levels of 15 variables.

So, 43 variables (III-VII clusters) respond to the action of adaptogens according to the "law of the initial level": increase of decreased and decrease of increased in the absence of significant changes of initially normal levels [Balanovs'kyi VP et al., 1993; Kolyada TI et al., 1995]. At the same time, 4 initially elevated and 9 normal variables show further growth.

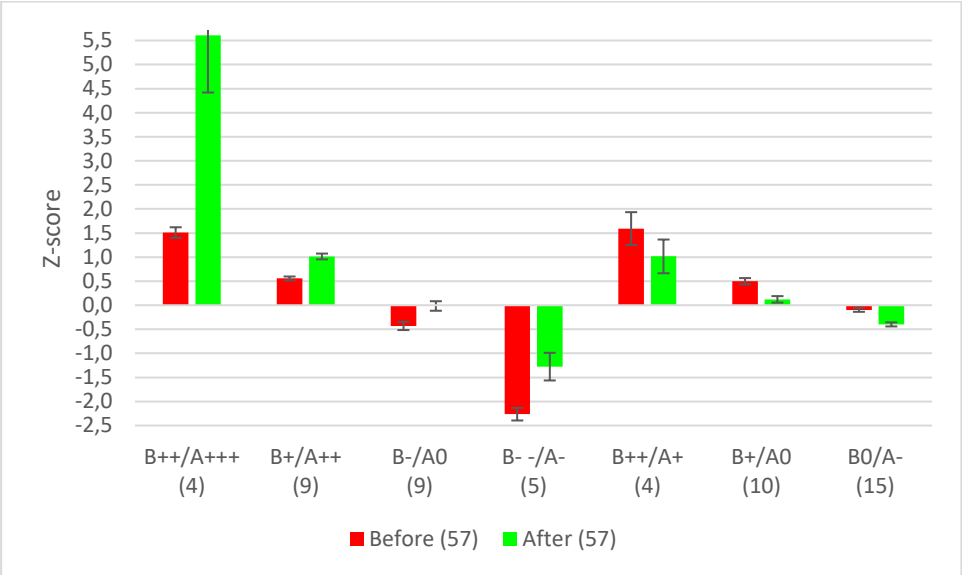


Fig. 3. Clusters of modulating effects (Z±SE) of adaptogens. The number of variables in the cluster is indicated in parentheses

Our many years of experience show that the calculation of mean direct differences between variables is a more sensitive test for evaluating the effect than the comparison of mean values. The use of this approach visualizes striking differences between the reactions of individual parameters, so pronounced that for ease of consideration, less pronounced adaptogenic effects are separated from drastic effects (Figs. 4 and 5).

It is known that the relationship between EEG and HRV parameters, as markers of the electrical activity of cortical, subcortical and stem neurons, is bilateral [Popovych IL et al, 2014]. Neuro-endocrine and neuro-immune connections are also bilateral [Akmayev PG, 1996]. That is, in the statistical analysis of relationships, the division into factorial (causal) and effective (consequential) signs (variables) is conditional (artificial).

However, neuro-endocrine variables precede immune and biophysical variables in effect profiles. However, neuro-endocrine variables precede immune, metabolic and biophysical variables in effect profiles.

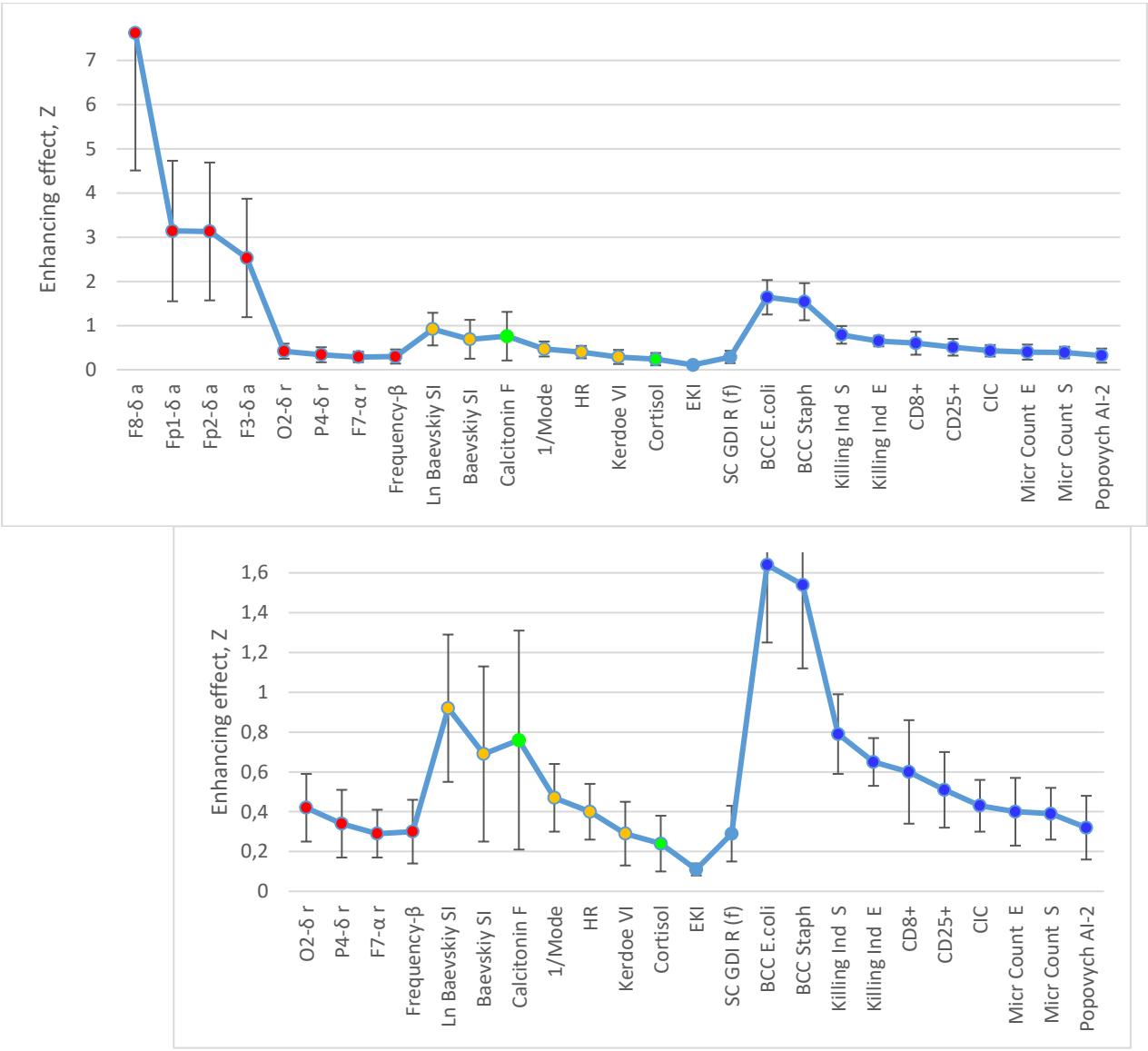


Fig. 4. Enhancing/upregulating effects of adaptogens

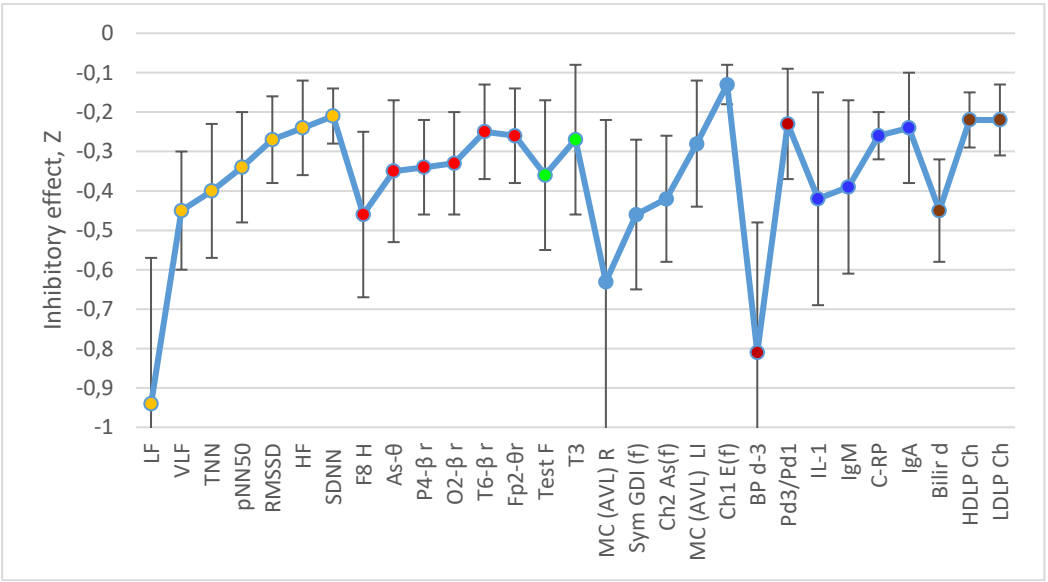


Fig. 5. Inhibitory/downregulating effects of adaptogens

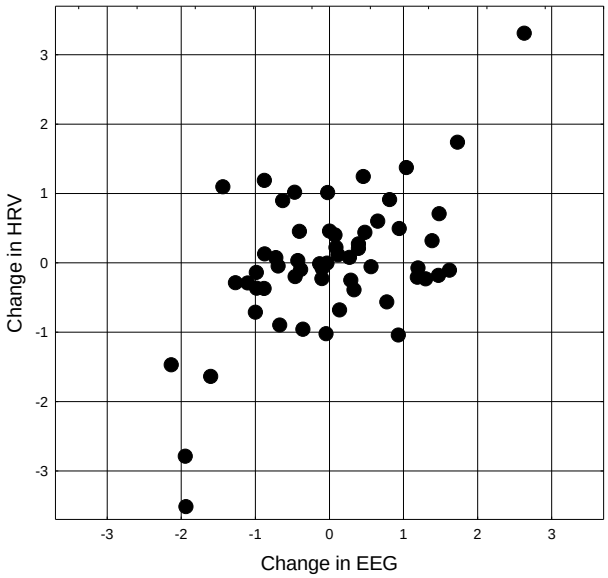
Analysis of the canonical correlation between EEG and HRV parameters shows that the α-rhythm generating structures, which are projected on the F7 locus, downregulate both sympathetic and vagal markers (Table 3). Instead the β-rhythm generating structures, which are projected on the P4 locus, downregulate vagal markers only. And vice versa, δ-rhythm generating structures, which are projected on the P4 and F3 loci, upregulate vagal markers. Taken together, changes in the activity of cortical nuclei determine changes in the activity of vagal and sympathetic nuclei by 31% (Fig. 6).

Table 3. Factor structure of canonical roots of changes in EEG and HRV variables

	left set
Variable	R
F3D	-0,261
F7A%	0,932
P4B%	0,383
P4D%	-0,220

	right set
Variable	R
BSI	-0,601
lnBSI	-0,309
HR	-0,566
pNN50	-0,347
LF	-0,408
HF	-0,543

	Correlations, left set with right set					
variable	BSI	lnBSI	HR	pNN50	LF	HF
F3D	-0,031	-0,097	0,012	0,174	0,208	0,164
F7A%	-0,303	-0,141	-0,326	-0,184	-0,165	-0,258
P4B%	-0,011	0,077	-0,008	-0,205	-0,284	-0,229
P4D%	-0,117	-0,214	-0,017	0,238	0,218	0,169



R=0,559; R^2=0,312; $\chi^2_{(24)}$=29,4; p=0,204; Λ Prime=0,558

Fig. 6. Scatterplot of canonical correlation between change in EEG (X-line) and HRV (Y-line) variables

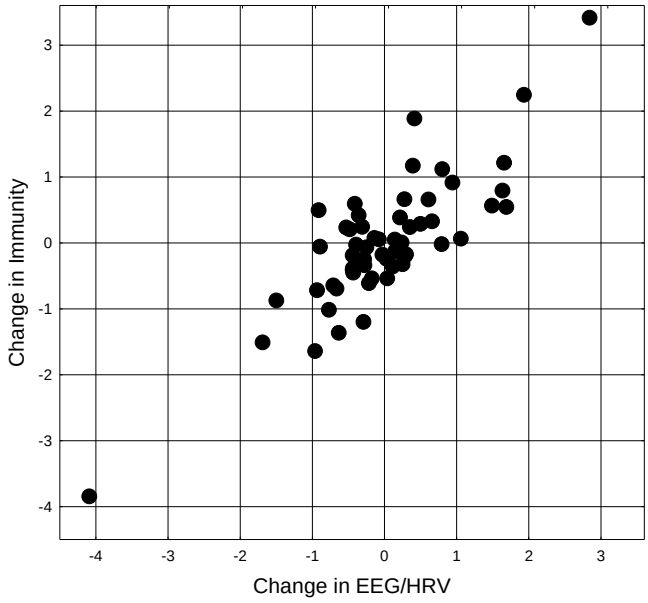
Changes in electrical activity of the CNS and ANS caused by adaptogens, in turn, determine changes in 12 immune parameters by 70% (Tables 4 and 5, Fig. 7).

Table 4. Matrix correlations between change in HRV/EEG and Immunity variables

Root Variable	Correlations, left set with right set											
	CD25	CD8	CIC	IgA	IgM	MC St	KI St	BC St	MC E	KI E	BC E	PAI-2
TNN	0,02	0,09	-0,04	-0,19	-0,02	-0,27	-0,14	-0,24	-0,11	-0,08	-0,17	-0,10
Mode	0,03	0,08	-0,42	-0,34	0,23	-0,21	-0,50	-0,34	-0,15	-0,07	-0,05	-0,20
BSI	-0,12	-0,08	-0,06	0,17	-0,33	0,15	0,11	0,16	0,23	-0,08	0,09	-0,01
Ln BSI	-0,06	-0,05	-0,02	0,17	-0,27	0,33	0,12	0,24	0,17	-0,03	0,10	0,02
VLF	0,17	0,15	0,03	-0,09	0,03	-0,45	-0,04	-0,26	0,10	-0,14	-0,04	0,00
BF	-0,01	-0,02	0,03	0,06	0,02	0,02	-0,25	-0,08	0,05	-0,23	0,00	0,03
Fp1D	-0,13	-0,27	-0,18	0,32	0,06	0,01	0,01	0,09	0,14	0,02	0,21	0,15
Fp2D	-0,32	-0,44	-0,17	0,36	0,14	0,08	0,08	0,22	0,09	0,03	0,24	0,03
F3D	-0,13	-0,35	-0,19	0,29	0,03	-0,07	-0,03	-0,05	-0,02	-0,14	-0,07	0,07
F8H	0,05	0,14	0,05	-0,27	-0,02	-0,06	0,03	0,01	-0,24	0,15	-0,08	-0,13
F8D	-0,05	-0,15	-0,15	0,27	0,09	-0,01	0,08	0,11	0,34	0,06	0,36	0,11
T6B%	0,19	0,35	0,08	-0,16	0,03	-0,12	0,15	0,04	-0,16	0,26	0,02	0,14
O2B%	0,06	0,09	0,15	0,08	-0,04	-0,22	-0,00	-0,14	-0,10	-0,03	-0,10	0,04

Table 5. Factor structure of canonical roots of changes in EEG/HRV and Immune variables

Change in HRV/EEG parameters	**R**
Fp2-δ PSDa	**0,547**
F3-δ PSDa	**0,519**
Fp1-δ PSDa	**0,425**
1/Mode HRV	**0,420**
F8-δ PSDa	**0,219**
Ln Baevskiy's St Index	**0,206**
Baevskiy's Stress Index	**0,058**
TNN HRV	**-0,341**
PSD VLF band	**-0,304**
T6-β PSDr	**-0,267**
O2-β PSDr	**-0,057**
Frequency-β	**-0,044**
F8 PSD Entropy	**-0,249**
Change in Immune parameters	**R**
Microbial Count vs E. coli	**-0,320**
$CD3^+CD8^+$ T-cytolytic Lymphoc	**-0,660**
$CD3^+CD25^+$ T-regulatory Lymph	**-0,390**
Bactericidity vs E. coli	**-0,167**
Killing Index vs E. coli	**-0,095**
Immunoglobulins A	**0,561**
Bactericidity vs Staph. aureus	**0,259**
Microbial Count vs Staph. aureus	**0,249**
Killing Index vs Staph. aureus	**0,173**
Popovych's Adaptation Index-2	**0,210**
Immunoglobulins M	**0,091**
Circulating Immune Complexes	**0,064**



R=0,837; R^2=0,701; $\chi^2_{(156)}$=214; p=0,00015; Λ Prime=0,0069
Fig. 7. Scatterplot of canonical correlation between change in EEG/HRV (X-line) and Immune (Y-line) variables

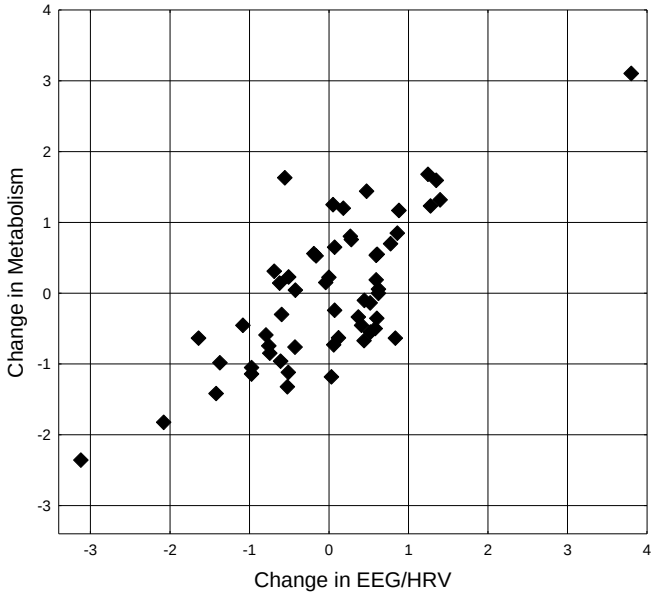
The rate of neurogenic determination of metabolic effects is 55% (Tables 6 and 7, Fig. 8).

Table 6. Matrix correlations between change in HRV/EEG and Metabolic, Hemodynamic and GDV variables

	Correlations, left set with right set										
Root Variable	C-RP	IL-1	HDLP Ch	LDLP Ch	Bilir direct	BP D-3	BPD3/ BPD1	SC GDI R(f)	Symm etry(f)	Kerdoe VI	HR
VLF	0,04	-0,01	0,06	-0,04	-0,25	-0,09	-0,113	-0,01	0,01	-0,05	-0,30
Mode	0,24	-0,02	0,13	0,06	-0,16	0,09	-0,140	-0,00	-0,12	-0,48	-0,76
Asym T	-0,26	0,12	0,04	-0,22	-0,20	-0,02	-0,133	0,05	-0,07	0,02	0,05
Fp1D	-0,09	0,20	-0,05	0,04	-0,16	-0,12	-0,118	-0,03	-0,05	0,12	0,16
Fp2D	-0,15	0,31	-0,21	0,08	-0,15	-0,07	-0,139	0,05	0,10	0,11	0,19
F3D	-0,07	0,26	-0,08	0,08	-0,16	-0,00	-0,127	-0,09	-0,02	0,01	0,01
F8D	-0,15	0,13	-0,05	0,01	-0,25	-0,09	-0,114	0,04	-0,03	0,12	0,17
Fp2T%	0,01	-0,08	-0,01	0,01	-0,28	-0,28	-0,177	-0,07	0,15	-0,07	-0,01
T6B%	-0,18	-0,34	-0,00	-0,10	0,16	0,09	0,112	0,13	0,04	-0,08	-0,00
P4D%	0,09	0,07	-0,27	0,21	0,03	0,13	-0,080	-0,01	-0,05	-0,06	-0,02
O2D%	0,17	0,11	-0,12	0,19	-0,11	-0,01	-0,097	-0,07	-0,14	-0,17	-0,15
TNN	0,03	-0,07	-0,07	-0,08	-0,04	-0,26	-0,304	-0,26	0,31	-0,34	-0,50
BSI	0,01	0,04	-0,10	0,14	-0,02	-0,12	0,174	0,03	-0,11	0,30	0,56
SDNN	0,02	0,00	0,07	-0,10	-0,05	-0,10	-0,318	-0,04	0,26	-0,28	-0,41
RMSSD	-0,02	-0,03	-0,01	-0,10	-0,06	-0,02	-0,240	0,00	0,21	-0,23	-0,45
F7A%	0,05	-0,02	0,17	-0,08	0,14	0,14	-0,066	-0,08	-0,11	-0,23	-0,33
BF	0,11	-0,05	-0,15	0,07	0,07	-0,19	0,058	0,23	0,09	0,23	0,06

Table 7. Factor structure of canonical roots of changes in EEG/HRV and Metabolic variables

EEG/HRV variables	R
F8-δ PSDa	-0,391
Fp2-δ PSDa	-0,389
F3-δ PSDa	-0,358
Fp2-θ PSDr	-0,319
Fp1-δ PSDa	-0,307
O2-δ PSDr	-0,265
PSD VLF band	-0,258
Asymmetry-θ	-0,198
P4-β PSDr	-0,178
P4-δ PSDr	-0,128
T6-β PSDr	0,316
1/Mode HRV	0,150
Metabolic variables	R
Bilirubin direct	0,856
HDLP Cholesterol	0,229
LDLP Cholesterol	-0,345
Interleukin-1	-0,301
C-reactive Protein	-0,130



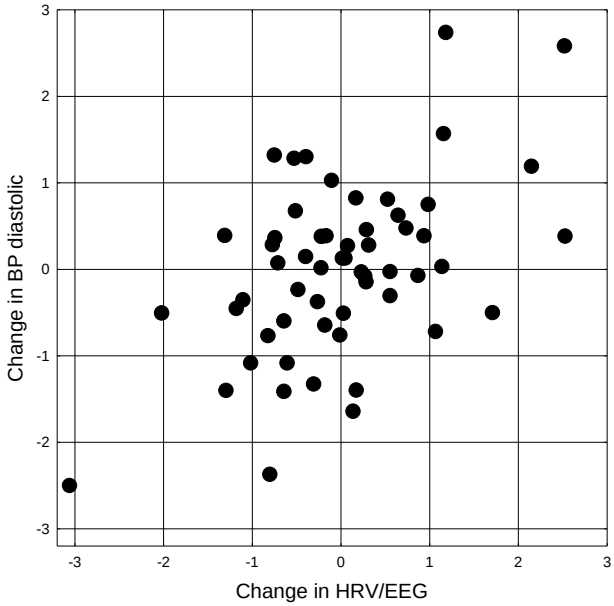
R=0,744; R^2=0,554; $\chi^2_{(60)}$=88; p=0,011; Λ Prime=0,155

Fig. 8. Scatterplot of canonical correlation between change in EEG/HRV (X-line) and Metabolic (Y-line) variables

It was found that diastolic (but not systolic) blood pressure, and only after the third consecutive registration, as well as its relation to the level after the first registration, are downregulated by θ-rhythm generating structures that project to the Fp2 locus and by vagal influences (Tables 6 and 8, Fig. 9).

Table 8. Factor structure of canonical roots of changes in EEG/HRV and Blood Pressure diastolic variables

HRV/EEG variables	R
TNN HRV	0,596
Fp2-θ PSDr	0,564
SDNN HRV	0,320
RMSSD HRV	0,138
Hemodynamics variables	R
Blood Pressure Diastolic-3	-0,977
BPD3/BPD1	-0,530



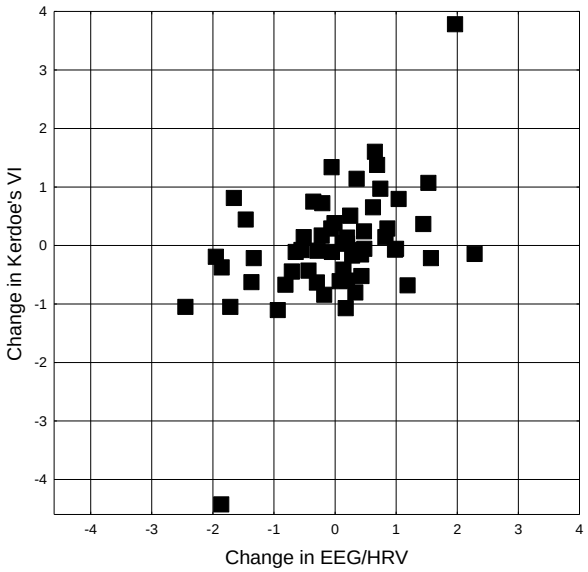
R=0,512; R^2=0,262; $\chi^2_{(12)}$=21,3; p=0,046; Λ Prime=0,661

Fig. 9. Scatterplot of canonical correlation between change in HRV/EEG (X-line) and Blood Pressure diastolic (Y-line) variables

Of particular note is the good old Kerdoe's Vegetative Index, which was widely used before the HRV era. It was found (Tables 6 and 9, Fig. 10) that its changes are negatively correlated with changes of HRV-markers of vagal tone as well as with α-rhythm generating structures that project to the F7 locus, on the contrary, positively correlated with changes of Baevskiy's Stress Index as marker of sympathetic tone as well as with frequency of β-rhythm. So, Kerdoe's Vegetative Index significant (but weak) reflect sympatho-vagal balance, but in its physiological essence it is, in my opinion, still a parameter of hemodynamics subject to regulation by both the ANS and the CNS.

Table 9. Factor structure of canonical roots of changes in HRV/EEG variables and Kerdoe's Vegetative Index

EEG/HRV variables	R
TNN HRV	0,720
SDNN HRV	0,607
RMSSD HRV	0,495
F7-α PSDr	0,493
Baevskiy's Stress Index	-0,631
Frequency-β	-0,502
Kerdoe's Vegetative Index	-1



R=0,468; R^2=0,219; $\chi^2_{(6)}$=12,9; p=0,045; Λ Prime=0,781

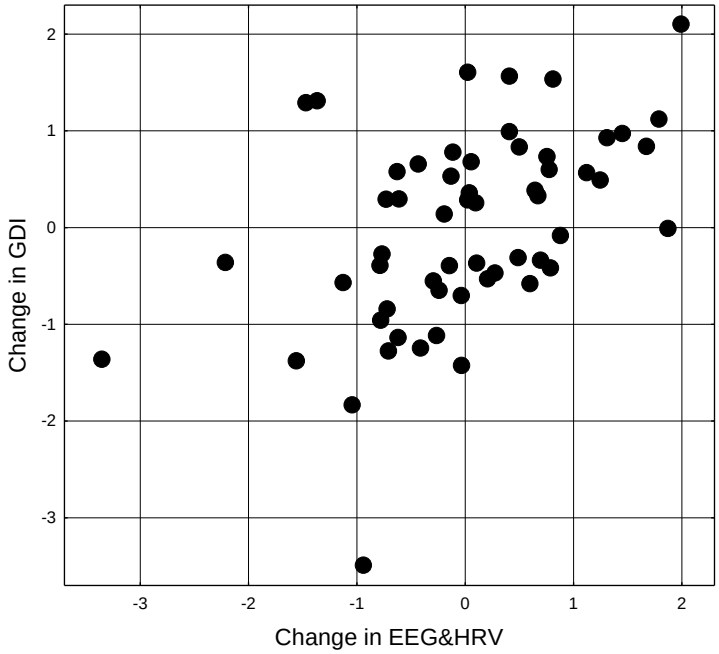
Fig. 10. Scatterplot of canonical correlation between change in HRV/EEG variables (X-line) and Kerdoe's Vegetative Index (Y-line)

Connections between changes in the neural and biophotonics parameters need the same special attention. In our laboratory have been shown that exist significant canonical correlation between parameters of biophotonics and principal neuroendocrine factors of adaptation [Babelyuk VY et al., 2017; 2021c; 2022] as well as parameters of EEG, HRV, hormones [Babelyuk VY et al., 2021c], leukocytogram [Babelyuk VY et al., 2021b], immunity [Babelyuk VY et al., 2021] and phagocytosis [Babelyuk VY et al., 2021a].

It was found (Tables 6 and 10) that adaptogen-induced changes in the Fractality (Shape Coefficient) of the gas discharge image (GDI) in Right projection are directly related to changes in the frequency of the β-rhythm and the activity of its generating structures, which are projected onto the P4 locus, but inversely to changes in vagal tone. Instead, the dynamics of GDI Symmetry and the Energy of the first virtual Chakra correlate with these parameters in the opposite way. In general, the parameters of biophotonics are determined by neural influences by 23% (Fig. 11).

Table 10. Factor structure of canonical roots of changes in EEG/HRV and GDV variables

EEG/HRV variables	**R**
Frequency-β	**-0,598**
P4-β PSDr	**-0,344**
TNN HRV	**0,367**
Biophotonics variables	**R**
Shape Coefficient GDI Right (f)	**-0,952**
Chakra 1 Energy (f)	**0,496**
Symmetry GDI (f)	**0,150**



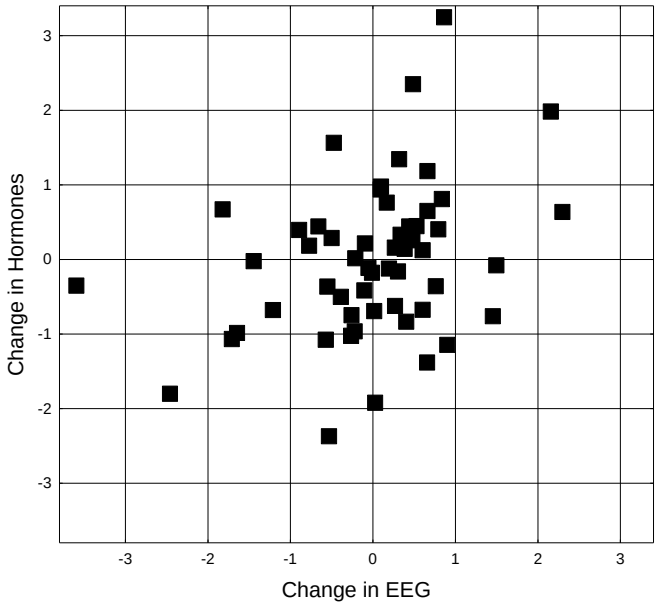
R=0,483; R^2=0,233; $\chi^2_{(12)}$=20,0; p=0,067; Λ Prime=0,681

Fig. 11. Scatterplot of canonical correlation between change in EEG/HRV (X-line) and Biophotonics (Y-line) variables

Despite reasonable expectations, at this stage of the analysis we were not lucky enough to find significant relationships between changes in EEG parameters and plasma hormones levels (Table 11 and Fig. 12).

Table 11. Factor structure of canonical roots of changes in EEG/HRV and Metabolic, Hemodynamic and GDV variables

EEG variables	**R**
F8-δ PSDa	**-0,591**
Fp2-δ PSDa	**-0,538**
Fp1-δ PSDa	**-0,444**
Asymmetry-θ	**0,662**
Endocrine variables	**R**
Testosterone standardized	**-0,769**
Cortisol	**-0,558**



R=0,338; R^2=0,114; $\chi^2_{(8)}$=9,7; p=0,285; Λ Prime=0,831

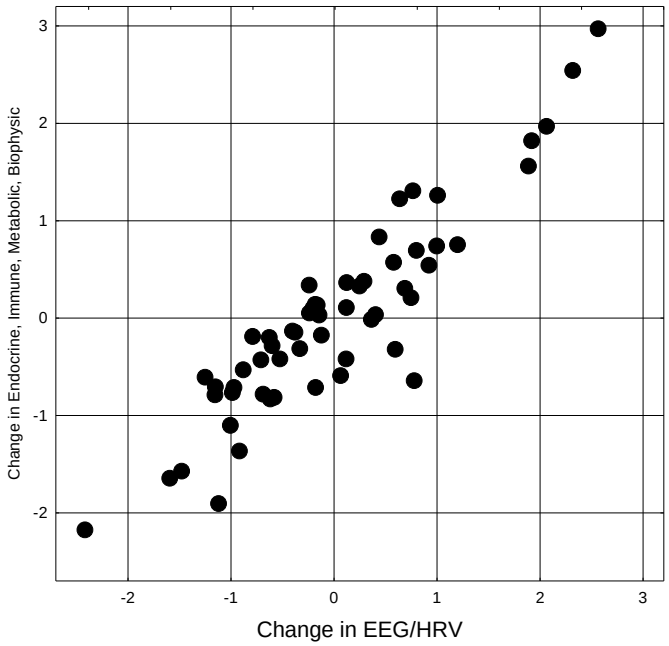
Fig. 12. Scatterplot of canonical correlation between change in EEG (X-line) and Endocrine (Y-line) variables

However, as a result of the total canonical correlation analysis, testosterone (both actual and standardized by sex and age) and cortisol still ended up in the factor structure of the root of regulated (dependent) variables, together with 10 immune, 2 hemodynamics, 3 metabolic and 3 biophotonics variables (Table 12). The regulating (causal) canonical root receives positive factor loadings from the δ-rhythm generating structures projected onto the Fp2, Fp1 and F3 loci, Baevskiy's Stress Index as a marker of sympathetic tone, 1/Mode as a marker of circulating catecholamines, as well as the VLF band of HRV. Other inverse components of the factor structure of the causal root are generating θ-, α- and β-rhythms neural structures, which are projected on Fp2, F7 and T6 loci respectively. But the maximum negative load is given by EEG Entropy in locus F8.

Table 12. Factor structure of canonical roots of changes in EEG/HRV and other variables

EEG/HRV variables	R
1/Mode HRV	0,495
Fp2-δ PSDa	0,445
F3-δ PSDa	0,434
Fp1-δ PSDa	0,416
Ln Baevskiy's Stress Index	0,231
Baevskiy's Stress Index	0,084
PSD VLF band	0,076
F8 PSD Entropy	-0,511
TNN HRV	-0,508
Fp2-θ PSDr	-0,316
F7-α PSDr	-0,185
SDNN HRV	-0,137
RMSSD HRV	-0,129
T6-β PSDr	-0,163
Endocrine, Immune, Metabolic, Hemo-dynamics, Biophotonics variables	**R**
Immunoglobulins A	0,468
Kerdoe's Vegetative Index	0,326
Testosterone standardized	0,320
Shape Coefficient GDI Right (f)	0,297
Killing Index vs Staph. aureus	0,293
Popovych's Adaptation Index-2	0,282
Interleukin-1	0,220
Microbial Count vs E. coli	0,220
Blood Pressure Diastolic-3	0,195
Testosterone actual	0,185
Bactericidity vs Staph. aureus	0,180
Circulating Immune Complexes	0,159
Bactericidity vs E. coli	0,140
Microbial Count vs Staph. aureus	0,107
HDLP Cholesterol	0,055
$CD3^+CD8^+$ T-cytolytic Lymphoc	-0,289
C-reactive Protein	-0,255
Symmetry GDI (f)	-0,104
Cortisol	-0,074
Chakra 1 Energy (f)	-0,038
$CD3^+CD25^+$ T-regulatory Lymph	-0,034

Taken together, adaptogen-induced changes in the activity of cortical, subcortical, and brainstem structures determine changes in endocrine, hemodynamics, metabolic, immune and biophotonics parameters by 83,5% (Fig. 13).



R=0,914; R^2=0,835; $\chi^2_{(308)}$=357; p=0,028; Λ Prime<10^{-4}
Fig. 13. Scatterplot of canonical correlation between change in EEG/HRV (X-line) and Endocrine, Immune, Metabolic. Hemodynamics and Biophotonics (Y-line) parameters

Discriminant analysis [Klecka WR, 1989] makes it possible to identify exactly those parameters from among those registered, according to the totality of which the integral state of persons before and after the use of adaptogens is significantly different. The forward stepwise program included 20 variables in the discriminant model: 7 EEGs related to **δ-, θ-, α-** and **β** rhythms as well as **entropy**, 8 **immune** and one representative each of **vegetative balance**, **hormones**, **metabolism**, **acupuncture points**, and **blood pressure** (Tables 13 and 14).

Table 13. Discriminant Function Analysis Summary
Step 20, N of vars in model: 20; Grouping: 2 grps;
Wilks' Lambda: 0,4904; approx. $F_{(21)}=4,8$; $p<10^{-6}$

Variables currently in the model	Groups (n) and Means±SE			Parameters of Wilks' Statistics					
	Before (57)	After (57)	*Effect (57)*	Wilks' Λ	Partial Λ	F-remove (1,93)	p-level	Tolerancy	Refer Cv **SD**
Killing Index vs Staph. aur., %	40,5 1,0	47,1 1,2	*+6,6* *1,7*	0,581	0,844	17,2	10^{-4}	0,352	58,9 0,142
Bactericidity vs E. coli, 10^9 B/L	77 4	93 3	*+16* *4*	0,540	0,910	9,35	0,003	0,149	99 0,100
Frequency-β, Hz	17,1 0,4	18,4 0,6	*+1,33* *0,68*	0,516	0,951	4,84	0,030	0,803	17,9 0,244
F7-α PSD, %	21,1 1,9	25,2 2,1	*+4,1* *1,8*	0,532	0,922	7,82	0,006	0,504	27,6 0,522
F8 PSD Entropy	0,793 0,024	0,718 0,035	*-0,075* *0,034*	0,491	0,998	0,15	0,699	0,502	0,815 0,202
O2-δ PSD, %	29,7 2,7	36,7 3,3	*+7,0* *2,8*	0,499	0,983	1,58	0,212	0,514	22,8 0,720
$CD3^+CD25^+$ T-regul. Lym, %	17.4 0.3	18.7 0.5	*+1.3* *0.5*	0,503	0,975	2,37	0,127	0,429	16,4 0,153
Kerdoe's Vegetative Index, un	-16,8 3,0	-9,6 3,8	*+7,2* *3,9*	0,536	0,915	8,67	0,004	0,735	-15 **25**
Bactericidity vs St. aur, 10^9 B/L	83 4	99 4	*+16* *4*	0,528	0,928	7,20	0,009	0,105	106 0,100
Pd3/Pd1 Ratio	1,001 0,007	0,992 0,009	*-0,018* *0,011*	0,511	0,960	3,87	0,052	0,787	0,998 0,079
F3-δ PSD, $\mu V^2/Hz$	235 41	478 149	*+242* *128*	0,507	0,966	3,23	0,075	0,599	98 0,981
CIC, units	32,9 2,0	40,4 2,3	*+7,2* *2,2*	0,497	0,987	1,22	0,273	0,629	45,0 0,389
IgA, g/L	1,96 0,07	1,89 0,07	*-0,08* *0,04*	0,495	0,990	0,93	0,336	0,597	1,875 0,167
Interleukin-1, ng/L	4,99 0,15	4,67 0,20	*-0,33* *0,21*	0,504	0,974	2,50	0,117	0,446	4,51 0,173
AP MC (AVL) EC LI, %	+0,29 0,19	-0,24 0,23	*-0,53* *0,30*	0,509	0,964	3,44	0,067	0,789	0,04 **1,91**
Asymmetry-θ, %	34 3	27 2	*-6,6* *3,5*	0,510	0,962	3,66	0,059	0,711	27,8 0,684
Microb. Count vs St. aur, B/Ph	58,4 1,0	62,3 1,2	*+3,9* *1,3*	0,506	0,970	2,92	0,091	0,450	61,6 0,160
Fp2-θ PSD, %	10,2 0,8	8,6 0,5	*-1,61* *0,76*	0,498	0,984	1,50	0,224	0,707	9,9 0,620
Microb. Count vs E. coli, B/Ph	61,2 1,4	65,4 1,3	*+4,2* *1,8*	0,496	0,988	1,09	0,298	0,387	54,7 0,194
Cortisol at all, nM/L	289 14	315 17	*+27* *16*	0,507	0,966	3,24	0,075	0,749	370 0,303
Cortisol at Female, nM/L	274 11	334 26	*+60* *24*						
Cortisol at Male, nM/L	304 27	297 21	*-7* *19*						

Notes. In each column, the first line is the average, the second – SE. In norm column - the average and Cv or ***SD***. The "*Effect*" and "*Norm*" columns are not the result of discriminant analysis

Table 14. Summary of stepwise analysis of discriminant variables ranked by Wilks' Λ criterion

Variables currently in the model	F to enter	p-level	**Λ**	F-value	p-level
Killing Index vs Staph. aur., %	18,7	10^{-4}	0,857	18,7	10^{-4}
Bactericidity vs E. coli, 10^9 Bac/L	5,46	0,021	0,816	12,5	10^{-4}
Frequency-β, Hz	4,80	0,030	0,782	10,2	10^{-5}
F8-α PSD, %	4,21	0,043	0,753	8,93	10^{-5}
F8 PSD Entropy	8,03	0,005	0,701	9,21	10^{-6}
O2-δ PSD, %	4,28	0,041	0,674	8,62	10^{-6}
$CD3^+CD25^+$ T-Lymphocyt, %	3,44	0,066	0,653	8,05	10^{-6}
Kerdoe's Vegetative Index, un	4,13	0,045	0,628	7,77	10^{-6}
Bactericidity vs St. aur, 10^9 Bac/L	3,73	0,056	0,606	7,50	10^{-6}
BPd3/BPd1 Ratio	2,90	0,091	0,590	7,16	10^{-6}
F3-δ PSD, $\mu V^2/Hz$	2,28	0,134	0,577	6,80	10^{-6}
CIC, units	2,03	0,157	0,566	6,47	10^{-6}
IgA, g/L	1,93	0,167	0,555	6,17	10^{-6}
Cortisol, nM/L	1,60	0,208	0,546	5,88	10^{-6}
Interleukin-1, ng/L	1,66	0,201	0,537	5,64	10^{-6}
AP MC (AVL) EC LI, %	1,85	0,177	0,527	5,44	10^{-6}
Asymmetry-θ, %	2,92	0,090	0,511	5,40	10^{-6}
Microbial Count vs St. aur, B/Ph	1,41	0,238	0,504	5,20	10^{-6}
Fp2-θ PSD, %	1,44	0,233	0,496	5,02	10^{-6}
Microbial Count vs E. coli, B/Ph	1,09	0,298	0,490	4,83	10^{-6}

Interestingly, according to the Student's test, the differences between post and pre levels of 8 variables are insignificant, while according to the Wilks' statistics, the difference between the post- and pre-impact states is highly reliable ($p<10^{-6}$). On the other hand, a number of variables, despite their recognizable properties, were outside the discriminant model, apparently due to duplication and/or redundancy of information (Tables 15-17).

Table 15. HRV variables currently not in the discriminant model

Variables currently not in the model	Groups (n) and Means±SE			Parameters of Wilks' Statistics					
	Before (57)	**After (57)**	***Effect (57)***	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerancy	Refer Cv **SD**
PSD VLF band, msec²	1185 130	883 97	*-302* *106*	0,485	0,990	0,97	0,327	0,844	1298 0,564
PSD LF band, msec²	1085 145	786 88	*-299* *110*	0,486	0,991	0,87	0,352	0,838	674 0,470
PSD HF band, msec²	334 65	256 54	*-78* *38*	0,490	0,999	0,10	0,758	0,820	376 0,741
RMSSD HRV, msec	26,3 2,4	22,1 1,7	*-4,2* *1,4*	0,490	1,000	0,00	0,977	0,815	30,3 0,483
SDNN HRV, msec	48,8 2,8	42,8 2,2	*-6,0* *2,0*	0,487	0,993	0,62	0,434	0,817	56,5 0,524
pNN50, %	7,4 1,6	4,7 1,1	*-2,7* *1,0*	0,490	1,000	0,02	0,885	0,814	9,6 0,840
TNN HRV, units	11,6 0,6	10,6 0,5	*-0,96* *0,42*	0,490	0,998	0,15	0,697	0,836	11,2 0,217
Mode HRV, msec	802 18	755 20	*-47* *17*	0,490	1,000	0,00	1,000	0,418	871 0,115
HR, beats/min	74,2 1,5	77,5 1,5	*+3,3* *1,2*	0,486	0,990	0,91	0,343	0,454	68,8 0,119
Baevskiy's Stress Index, units	172 23	204 26	*+32* *25*	0,486	0,990	0,92	0,340	0,807	134 0,423
Baevskiy's Stress Index, ln units	4,83 0,10	5,01 0,10	*+0,18* *0,08*	0,487	0,993	0,61	0,436	0,794	4,89 0,224

Table 16. EEG and Endocrine variables currently not in the discriminant model

Variables currently not in the model	Groups (n) and Means±SE			Parameters of Wilks' Statistics					
	Before (57)	**After (57)**	***Effect (57)***	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerancy	Refer Cv **SD**
F8-δ PSD, μV²/Hz	174 34	754 248	*+580* *237*	0,489	0,996	0,34	0,561	0,384	92 1,642
Fp2-δ PSD, μV²/Hz	191 37	482 158	*+292* *145*	0,489	0,997	0,25	0,616	0,425	74 1,260
Fp1-δ PSD, μV²/Hz	195 45	435 139	*+239* *121*	0,490	1,000	0,04	0,850	0,430	58 1,132
P4-δ PSD, %	30,6 2,5	35,7 2,9	*+5,1* *2,5*	0,490	0,999	0,09	0,766	0,386	23,6 0,626
P4-β PSD, %	22,1 1,6	18,2 1,2	*-3,9* *1,4*	0,490	1,000	0,03	0,861	0,798	22,8 0,503
T6-β PSD, %	25,6 2,2	21,5 1,7	*-4,1* *2,0*	0,489	0,997	0,23	0,631	0,760	29,8 0,554
O2-β PSD, %	23,0 1,7	18,7 1,4	*-4,3* *1,7*	0,488	0,994	0,51	0,476	0,754	24,4 0,531
Triiodothyronine at Female, nM/L	2,23 0,16	2,03 0,16	*-0,20* *0,12*	0,488	0,996	0,37	0,543	0,684	2,20 0,227
Triiodothyronine at Male, nM/L	1,97 0,16	1,91 0,17	*-0,06* *0,14*	0,488	0,996	0,37	0,543	0,684	2,20 0,227
Testosterone at Female, nM/L	4,14 0,61	3,64 0,59	*-0,50* *0,27*	0,490	0,999	0,05	0,826	0,723	2,30 0,600
Testosterone at Male, nM/L	13,98 1,05	12,73 1,09	*-0,24* *0,84*	0,490	0,999	0,05	0,826	0,723	14,86 0,400
Calcitonin at Female, ng/L	7,80 1,17	9,85 1,39	*+2,05* *1,48*	0,486	0,990	0,91	0,343	0,454	5,50 0,493
Calcitonin at Male, ng/L	10,69 1,17	10,67 1,44	*-0,02* *1,88*	0,486	0,990	0,91	0,343	0,454	13,95 0,493
Aldosterone at all, pM/L	224,3 3,8	222,8 2,6	*-1,6* *4,0*	0,487	0,994	0,59	0,443	0,761	238 0,187

Table 17. Immune, Metabolic and Biophysic variables currently not in the discriminant model

Variables currently not in the model	Groups (n) and Means±SE			Parameters of Wilks' Statistics					
	Before (57)	After (57)	*Effect (57)*	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerancy	Refer Cv **SD**
Popovych's Adaptation Index-2, un.	0,89 0,05	1,03 0,06	*+0,14* *0,07*	0,488	0,995	0,42	0,518	0,827	1,705 0,245
IgM, g/L	1,47 0,05	1,36 0,05	*-0,11* *0,06*	0,486	0,991	0,81	0,369	0,762	1,15 0,239
Killing Index vs E. coli, %	35,5 0,9	41,8 1,0	*+6,3* *1,2*	0,490	1,000	0,02	0,899	0,240	62,0 0,156
$CD3^+CD8^+$ T-cytolytic Lymphoc, %	20,9 0,6	22,9 0,9	*+2,0* *0,8*	0,490	1,000	0,00	0,965	0,134	23,5 0,138
C-reactive Protein, µg/L	2,70 0,10	2,52 0,09	*-0,18* *0,04*	0,488	0,995	0,50	0,481	0,629	2,18 0,324
Bilirubin direct, µM/L	2,26 0,14	1,87 0,12	*-0,39* *0,11*	0,488	0,995	0,47	0,494	0,628	1,70 0,500
LDLP Cholesterol, mM/L	3,40 0,09	3,26 0,07	*-0,14* *0,06*	0,489	0,996	0,36	0,551	0,735	3,50 0,193
HDLP Cholesterol, mM/L	1,59 0,06	1,50 0,05	*-0,09* *0,03*	0,486	0,992	0,77	0,383	0,750	1,39 0,297
BP diastolic-3, mmHg	82,6 1,5	79,1 1,5	*-3,5* *1,4*	0,490	0,999	0,06	0,807	0,587	79 0,054
Electrokinetic Index, %	44,0 1,7	45,1 1,8	*+1,1* *0,3*	0,487	0,994	0,59	0,443	0,761	42,1 0,250
Chakra 1 Energy (f)	+0,24 0,04	+0,20 0,04	*-0,04* *0,02*	0,490	0,999	0,07	0,794	0,281	+0,10 **0,37**
Chakra 2 Asymmetry (f)	0,00 0,03	-0,13 0,04	*-0,13* *0,05*	0,490	0,999	0,05	0,816	0,446	-0,10 **0,31**
Shape Coefficient Right (f), units	13,90 0,20	14,37 0,21	*+0,47* *0,23*	0,487	0,994	0,58	0,449	0,830	14,3 0,114
Symmetry GDI (f), %	93,54 0,16	92,84 0,24	*-0,64* *0,76*	0,490	0,999	0,08	0,772	0,485	93,2 0,015

Calculating the value of the discriminant root for each patient by parameters reflects in table 18, allows visualization of each patient in the information space of the root (Fig. 15).

Table 18. Standardized and raw coefficients and constant for discriminant variables

Variables	Coefficients	
	Standar-dized	Raw
Killing Index vs Staph. aur., %	-0,932	-0,115
Bactericidity vs E. coli, 10^9 B/L	-1,097	-0,041
Frequency-β, Hz	-0,348	-0,089
F7-α PSD, %	-0,550	-0,036
F8 PSD Entropy	0,080	0,352
O2-δ PSD, %	-0,252	-0,011
$CD3^+CD25^+$ T-Lymphocytes, %	-0,337	-0,104
Kerdoe's Vegetative Index, un	-0,477	-0,019
Bactericidity vs St. aur, 10^9 B/L	1,158	0,041
Pd3/Pd1 Ratio	0,315	5,134
F3-δ PSD, $\mu V^2/Hz$	-0,332	-0,0004
CIC, units	-0,201	-0,012
IgA, g/L	0,181	0,343
Cortisol, nM/L	-0,297	-0,0025
Interleukin-1, ng/L	-0,339	-0,253
AP MC (AVL) EC LI, %	0,298	0,191
Asymmetry-θ, %	0,323	0,016
Microbial Count vs St. aur, B/Ph	-0,364	-0,043
Fp2-θ PSD, %	0,210	0,042
Microbial Count vs E. coli, B/Ph	0,243	0,024
Constant		5,852
Eigenvalue		1,039
Squared Mahalanobis Distance=4,08; $F_{(21)}$=4,83; $p<10^{-6}$		
Canonical R=0,714; Wilks' Λ=0,4904; $\chi^2_{(20)}$=73; $p<10^{-6}$		

As we can see, the reaction to both electrical stimulation and Naftussya water drinking takes place in all participants without exception, although the severity of the reaction has significant individual differences (Fig. 15), which is quite natural.

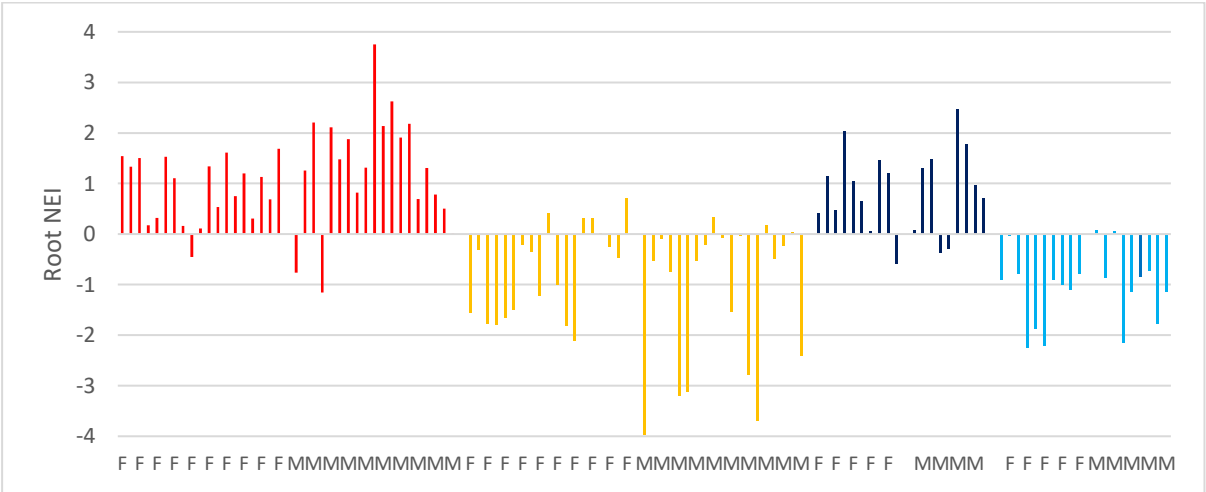


Fig. 15. Individual values of Roots of Female and Male before and after course of transcutaneous electrical stimulation and drinking of Naftussya water

Retrospective recognition of the integral state of patients by calculating the classification functions according to the coefficients and constants given in the table 19, with respect to the

initial state is with 6 errors, and with respect to the final state – with 10 errors (classification accuracy is 86%).

Table 19. Coefficients and constants of classification functions

Clusters	Before	After
Variables	**0,500**	**0,500**
Killing Index vs Staph. aureus, %	1,121	1,353
Bactericidity vs E. coli, 10^9 Bacteria/L	-0,125	-0,042
Frequency-β, Hz	2,381	2,561
F7-α PSD, %	-0,043	0,030
F8 PSD Entropy	19,23	18,52
O2-δ PSD, %	0,083	0,106
$CD3^+CD25^+$ T-Lymphocytes, %	5,302	5,512
Kerdoe's Vegetative Index, units	-0,219	-0,181
Bactericidity vs Staph. aur, 10^9 Bacteria/L	-0,101	-0,184
Pd3/Pd1 Ratio	285,9	275,5
F3-δ PSD, $\mu V^2/Hz$	0,0053	0,0061
Circulating Immune Complexes, units	0,274	0,299
IgA, g/L	10,90	10,20
Cortisol, nM/L	0,029	0,034
Interleukin-1, ng/L	11,58	12,09
AP MC (AVL) EC LI, %	-2,187	-2,572
Asymmetry-θ, %	-0,025	-0,057
Microbial Count vs Staph. aur., Bac/Phag	0,548	0,634
Fp2-θ PSD, %	0,495	0,410
Microbial Count vs E. coli, Bac/Phagocyte	0,450	0,401
Constants	-316,0	-327,8

No significant differences were found either for adaptogen nature or for both sexes (Figs. 16 and 17).

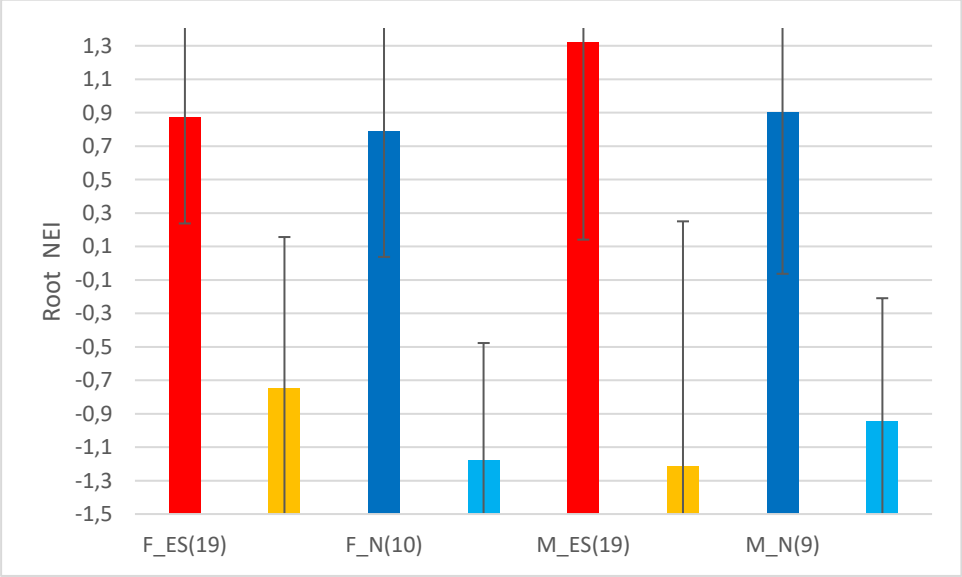


Fig. 16. Average values (Mean±SD) of the discriminant neuro-endocrine-immune root before and after course of transcutaneous electrostimulation and drinking of Naftussya water

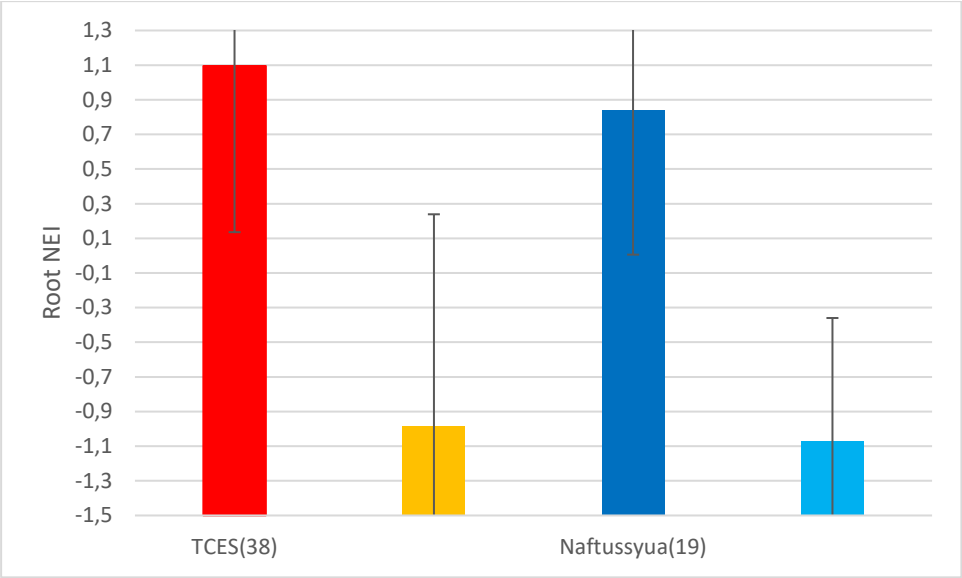


Fig. 17. Average values (Mean±SD) of the discriminant neuro-endocrine-immune root before and after course of transcutaneous electrostimulation and drinking of Naftussya water

A decrease in the level of the root reflects an increase in the levels of 13 variables related to the root inversely, and a decrease in the levels of 7 variables related to it directly (Table 21).

Table 21. Clusters of effects of adaptogens as differences between levels (Z±SE) after and before treatment

Clusters and Variables	R	Before (57)	After (57)	*Effect (57)*
B+/A+++				
F3-δ PSDa	-0,146	+1,44±0,42	+3,97±1,56	+2,53±1,34
F8-δ PSDa		+1,53±0,45	+9,14±3,24	+7,62±3,11
Fp2-δ PSDa		+1,26±0,39	+4,39±1,70	+3,13±1,56
Fp1-δ PSDa		+1,81±0,60	+4,95±1,83	+3,14±1,59
B+/A++				
O2-δ PSDr	-0,152	+0,42±0,17	+0,84±0,20	+0,42±0,17
$CD3^+CD25^+$ T-regulatory Lym	-0,193	+0,40±0,13	+0,90±0,20	+0,51±0,19
Microbial Count vs E. coli	-0,220	+0,61±0,13	+1,01±0,12	+0,40±0,17
P4-δ PSDr		+0,47±0,17	+0,82±0,20	+0,34±0,17
1/Mode HRV		+0,68±0,18	+1,16±0,20	+0,47±0,17
Heart Rate		+0,65±0,18	+1,06±0,18	+0,40±0,14
Baevskiy's Stress Index raw		+0,50±0,33	+1,18±0,45	+0,69±0,44
Calcitonin at Female		+0,85±0,31	+1,60±0,51	+0,76±0,55
Elektrokinetic Index		+0,42±0,13	+0,53±0,13	+0,11±0,03
B-/A0				
F7-α PSDr	-0,135	-0,45±0,13	-0,17±0,14	+0,29±0,12
Frequency-β	-0,166	-0,18±0,09	+0,12±0,14	+0,30±0,16
Kerdoe's Vegetative Index	-0,139	-0,08±0,12	+0,21±0,14	+0,29±0,16
Cortisol at all	-0,111	-0,72±0,13	-0,49±0,15	+0,24±0,14
Cortisol at Female		-0,85±0,10	-0,32±0,23	+0,53±0,21
Cortisol at Male		-0,59±0,24	-0,66±0,19	-0,07±0,17
Ln Baevskiy's Stress Index		-0,40±0,43	+0,52±0,43	+0,92±0,37
Shape Coefficient GDI Right (f)		-0,23±0,12	+0,06±0,13	+0,29±0,14
$CD3^+CD8^+$ T-cytolytic Lymph		-0,80±0,19	-0,20±0,27	+0,60±0,26
Microbial Count vs St. aureus	-0,225	-0,32±0,10	+0,07±0,13	+0,39±0,13
CIC	-0,231	-0,69±0,11	-0,26±0,13	+0,43±0,13
B- -/A-				
Bactericidity vs E. coli	-0,303	-2,27±0,36	-0,63±0,34	+1,64±0,39
Bactericidity vs Staph. aureus	-0,287	-2,16±0,35	-0,62±0,36	+1,54±0,42
Killing Index vs Staph. aureus	-0,401	-2,20±0,12	-1,42±0,14	+0,79±0,20
Killing Index vs E. coli		-2,74±0,09	-2,09±0,10	+0,65±0,12
Popovych's Adaptation Index-2		-1,95±0,13	-1,62±0,15	+0,32±0,16
B++/A+				
PSD LF band		+1,28±0,44	+0,34±0,26	-0,94±0,37
Testosterone at Female		+1,33±0,44	+0,97±0,43	-0,36±0,19
AP MC (AVL) Right EC		+2,61±0,44	+1,99±0,23	-0,63±0,41
IgM		+1,15±0,17	+0,76±0,18	-0,39±0,22
B+/A0				
Asymmetry-θ	0,158	+0,33±0,16	-0,02±0,13	-0,35±0,18
Interleukin-1	0,122	+0,62±0,19	+0,20±0,26	-0,42±0,27
IgA	0,071	+0,29±0,23	+0,04±0,22	-0,24±0,14
Symmetry GDI (f)		+0,24±0,11	-0,22±0,17	-0,46±0,19
Chakra 2 Asymmetry (f)		+0,32±0,10	-0,10±0,12	-0,42±0,16
Chakra 1 Energy (f)		+0,47±0,12	+0,33±0,12	-0,13±0,05
C-reactive Protein		+0,73±0,19	+0,48±0,26	-0,26±0,06
BP diastolic-3		+0,84±0,36	+0,03±0,36	-0,81±0,33
HDLP Cholesterol		+0,50±0,13	+0,28±0,11	-0,22±0,07
Bilirubin direct		+0,65±0,16	+0,20±0,14	-0,45±0,13

B0/A-				
F8 PSD Entropy	0,164	-0,14±0,15	-0,59±0,21	-0,46±0,21
Fp2-θ PSDr	0,160	+0,05±0,12	-0,21±0,09	-0,26±0,12
AP MC (AVL) EC Laterality In	0,166	+0,13±0,10	-0,14±0,12	-0,28±0,16
Pd3/Pd1 Ratio	0,145	+0,15±0,08	-0,08±0,12	-0,23±0,14
P4-β PSDr		-0,06±0,14	-0,40±0,10	-0,34±0,12
T6-β PSDr		-0,26±0,14	-0,50±0,11	-0,25±0,12
O2-β PSDr		-0,11±0,13	-0,44±0,11	-0,33±0,13
PSD VLF band		-0,14±0,18	-0,58±0,13	-0,45±0,15
PSD HF band		-0,18±0,22	-0,42±0,19	-0,24±0,12
RMSSD HRV		-0,23±0,19	-0,50±0,13	-0,27±0,11
SDNN HRV		-0,26±0,09	-0,47±0,07	-0,21±0,07
pNN_{50} HRV		-0,27±0,23	-0,61±0,14	-0,34±0,14
TNN HRV		+0,16±0,23	-0,23±0,22	-0,40±0,17
Triiodothyronine		-0,19±0,23	-0,46±0,23	-0,27±0,19
LDLP Cholesterol		-0,12±0,13	-0,34±0,10	-0,22±0,09

Given that full or partial **normalization of reduced** 5 parameters of phagocytosis, leukocytary Popovych's Adaptation index, as well as CIC and T-cytolytic lymphocytes are **definitely physiologically favorable** effects of adaptogens, accompanying moderate sympathotonic shifts of Baevskiy's and Kerdoe's indices within the normal range, a moderate increase in frequency β-rhythm, in lower limit levels of cortisol and activity of α-rhythm generating neurons (F7 locus, probably left insula?), as well as complete normalization of GDI Fractality in the right projection can also be interpreted as **physiologically favorable**.

On the other hand, definitely physiologically beneficial effects of adaptogens are full or partial **normalization of elevated** spectral power of LF band, electroconductivity of AP MC (AVL) Right, levels of IL-1, CRP, IgM, bilirubin direct, blood pressure diastolic as well as testosterone (at women, but not at men). Therefore, the accompanying normalization of the right-sided asymmetry of both θ-rhythm EEG and second Chakra as well as the transformation of the right-sided GDI asymmetry into the left-sided one are also probably **physiologically favorable** changes. A particularly interesting finding is the **decrease** in the **increased** energy of the first Chakra. According to Ayurvedic medicine, the first Chakra is related to the testicles [Puchko LG, 2004] or adrenals [Chase CR, 2018] (which are a source of testosterone in women), pelvic nerve plexus as well as large intestine; the second Chakra is related to the ovaries and adrenals or to testes/ovaries, inferior mesenteric ganglion as well as ileum. Against this background of physiologically favorable effects, a decrease, albeit within the normal range, of HDLP Cholesterol and IgA levels is dissonant.

The described changes are fully consistent with the concept of the normalizing (equilibrative) nature of adaptogenic effects.

At the same time, the upper limit levels of T-regulatory lymphocytes, microbial count of neutrophils and electrokinetic index (inverse marker of biological age) under the influence of adaptogens continue to grow within the normal range, i.e. a physiologically favorable enhancing effect takes place. Adhering to the accepted approach, the accompanying further increase within the norm of plasma levels of catecholamines (markers: 1/Mo HRV and HR) and calcitonin, activity of δ-rhythm generating neurons projected onto the P4 and O2 loci as well as drastical enhancing of activity of similar neurons projected onto the Fp1, Fp2, F3 and F8 loci, should also be considered physiologically favorable changes.

On the other hand, a decrease within the normal limits of the initially normal plasma levels of LDLP cholesterol and triiodothyronine, as well as potentiation of a consistent decrease in diastolic pressure in the process of three-time registration, are also very useful. Therefore, a leftward shift of symmetry of AP MC(AVL) electroconductivity; further moderate decrease in activity of β-rhythm generating neurons projected onto the P4, T6 and O2 loci; θ-rhythm

generating neurons projected onto the Fp2 locus; EEG Entropy in F8 locus as well as in vagal tone should be considered physiologically favorable.

If HRV parameters such as TNN, SDNN, RMSSD, pNN_{50} and HF are unconditional markers of vagal tone, then the LF and VLF bands are still a matter of debate. LF power may be produced by both the vagal and sympathetic, and blood pressure regulation via baroreceptors [Berntson CG et al., 2007], primarily by the vagal [Reyes del Paso GA et al., 2013] or by baroreflex activity alone [Goldstein DS et al., 2011]. In resting conditions, the LF band reflects baroreflex activity and not cardiac sympathetic innervation [Schaffer F et al, 2014; 2017].

Akselrod S et al [1981] in pioneering experiment on seven trained, conscious, unanesthetized dogs illustrated that after adequate parasympathetic blockade the LF (then it was nominated as mid-frequency) and HF peaks are abolished, while the amplitude of the VLF (was nominated as low-frequency) peak is reduced. Combined β-sympathetic and parasympathetic blockade abolishes all HR fluctuations leading to a metronome-like heartbeat. β-sympathetic blockade alone tends to reduce the VLF peak's amplitude, but this effect is not consistent because of the low tonic level of sympathetic activity in the resting dog. Increasing the activity of either the sympathetic (by vasodilator-induced decreasing arterial pressure) or parasympathetic (by vasoconstrictor-induced increasing blood pressure) nervous system augments the area under the VLF peak. Therefore, the PSNS mediates HR fluctuations at frequencies corresponding to the LF and HF peaks of the power spectrum, whereas both SNS and PSNS may mediate the VLF fluctuations. Selective adequate blockade of renin-angiotensin system (by converting enzyme inhibitor) lead to 2-4,5-fold increase in the area under the VLF peak. The authors concluded that sympathetic and parasympathetic nervous activity make frequency-specific contribution to the heart rate power spectrum, and that renin-angiotensin-[aldosterone] system activity strongly modulates the amplitude of the spectral peak located at 0,04 Hz. Taylor JA et al [1998] used blocking drugs to evaluate potential contribution of sympathetic and vagal mechanisms and the renin-angiotensin-aldosterone system to VLF (0,003 to 0,03 Hz) HRV in 10 young healthy subjects. Beta-adrenergic blockade had no significant effect on VLF or LF (0,05 to 0,15 Hz) power but increased HF (0,2 to 0,3 Hz) power 2-fold. ACE blockade had no significant effect on LF or HF power but modestly (approximately 21%) increased VLF power in the supine (but not upright tilt) position ($p<0,05$). The most profound effects were exerted by parasympathetic blockade: atropine, given alone or with atenolol, abolished nearly all HRV and decreased VLF HRV by 92%. Authors concluded that although VLF band are influenced by the renin-angiotensin-aldosterone system, as LF and HF bands, they depend primarily on the presence of parasympathetic outflow. Therefore, the prognostic value of VLF oscillations may derive from the fundamental importance of parasympathetic mechanisms in cardiovascular health. I literally just saw an article by Del Valle-Mandragon L et al. [2022] showing that during hemodialysis angiotensin II had a positive correlation with VLF (r=0,390) and with LF/HF (r=0,359) and a negative correlation with LF (r=-0,262) and HF (r=-0,383) bands. Low power in VLF band has been associated with high level of inflammation markers in several studies [Carney RM et al., 2007; Lampert R et al., 2008]. Finally, low VLF power has been correlated with low levels of testosterone, while other biochemical markers, such as those mediated by the hypothalamic–pituitary–adrenal axis (e.g., cortisol), have not [Theorell T et al., 2007; Hasson D et al., 2009]. So, the ambiguity of judgments about VLF continues. Taking into account the accompanying pattern of diastolic pressure reduction, I make an assumption that in this case, the decrease in VLF band power reflects, first of all, a decrease in vagal tone, plasma levels of proinflammatory mediators and testosterone (at women only), and to a lesser extent, in plasma levels of renin–angiotensin as well as endothelial vasoconstrictor factors.

According to the excellent concept of "central autonomic network (CAN)" (Benarroch EE, 1993; Palma JA & Benarroch EE, 2014; Thayer JF & Lane RD, 2009) it include following

cortical, subcortical, and medullary structures (Fig. 18): the anterior cingulate, insular, orbitofrontal, and ventromedial cortices; the central nucleus of the amygdala (CeA); the paraventricular and related nuclei of the hypothalamus; the periaqueductal gray matter; the nucleus of the solitary tract; the nucleus ambiguous; the ventrolateral medulla; the ventromedial medulla and the medullary tegmental field. The primary output of the CAN is mediated through the preganglionic sympathetic and parasympathetic neurons, which exert control over the heart via the stellate ganglia and the vagus nerve, respectively. The interplay of sympathetic and parasympathetic influences on sinoatrial node pacemaker activity generates the complex variability that characterizes the healthy heart rate rhythm, which is called HRV. A fundamental principle of the neural control of the heart is its hierarchical organization, with cortical structures providing inhibitory control over limbic and brainstem sympathoexcitatory, cardioacceleratory circuits. The prefrontal, cingulate, and insula cortices form an interconnected network with bi-directional communication with the amygdala. The amygdala is under tonic inhibitory control via prefrontal vagal pathways to intercalated cells in the amygdala. The activation of the CeA inhibits the nucleus of the solitary tract (NTS) which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons, and simultaneously inhibits vagal motor neurons in the nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVN). In addition, the CeA can directly activate the sympathoexcitatory neurons in the RVLM. Indeed, disruption of prefrontal activity leads to disinhibition of sympathoexcitatory circuits, with a resultant increase in heart rate and decrease in vagally-mediated HRV (Verberne AJ, 1996; Verberne AJ et al., 1997; Thayer GF & Lane RD, 2009).

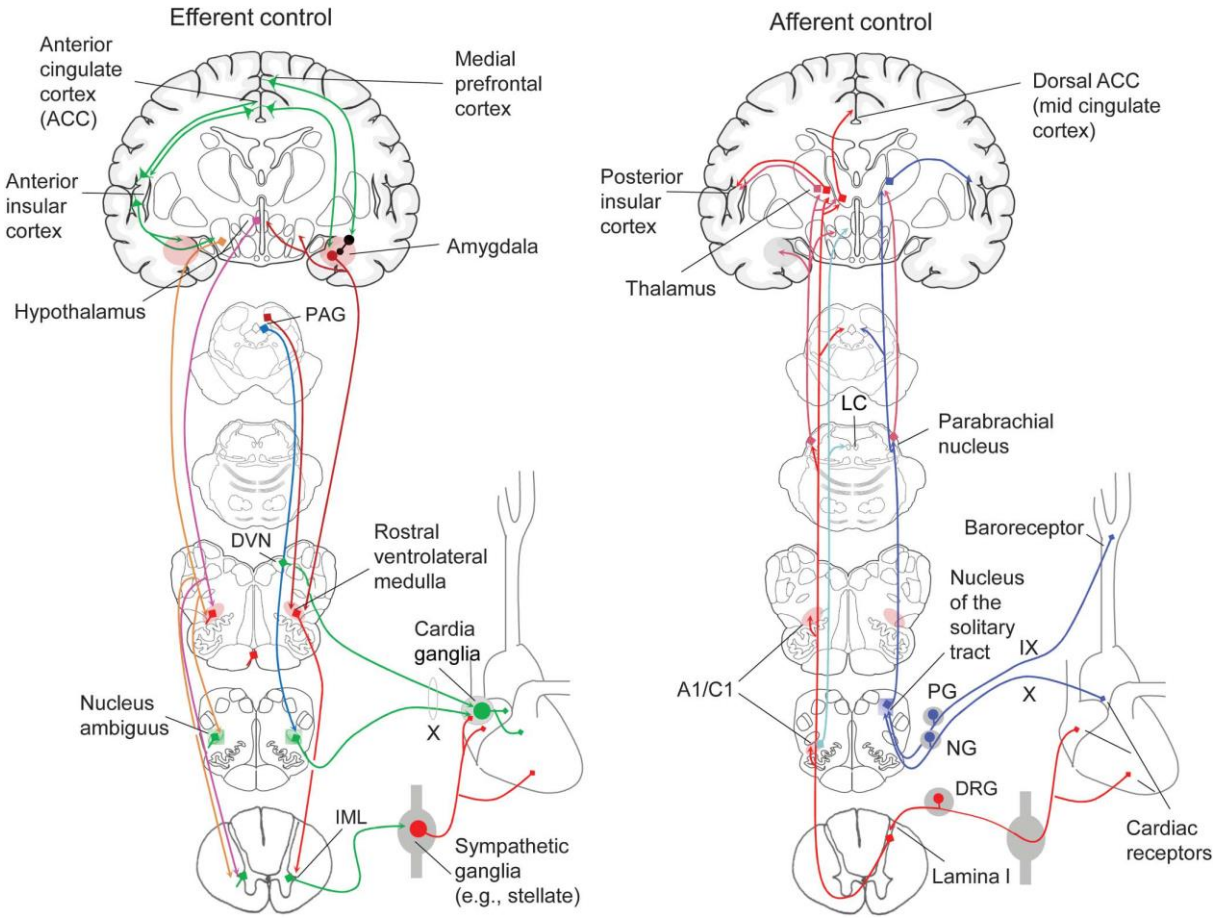


Fig. 18. Efferent and afferent control of cardiac function (Palma JE & Benarroch EE, 2014)

Mo J et al. [2019] presented their CAN visualization (Figs 19 and 20).

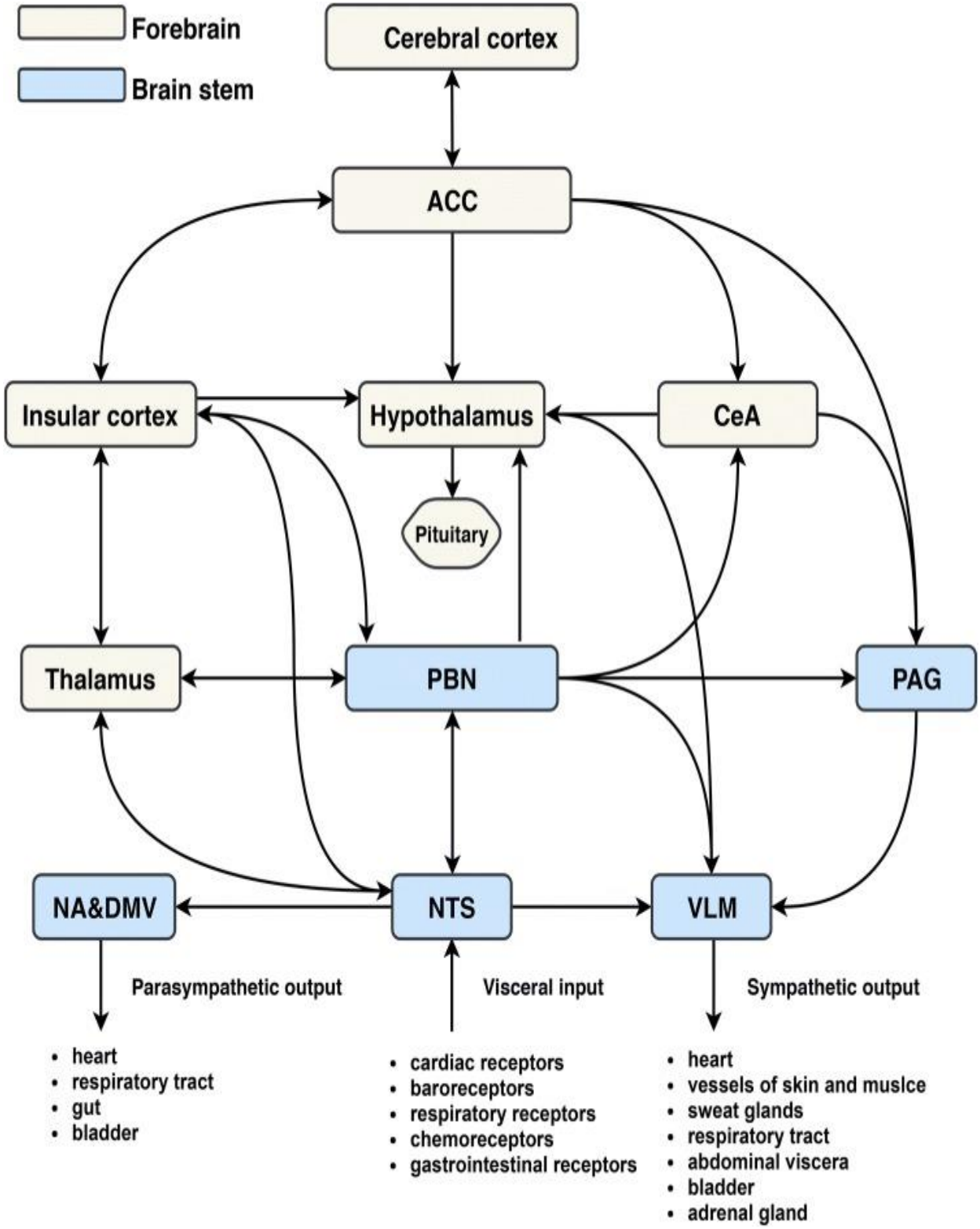


Fig. 19. Diagram of the central autonomic network

Visceral information is relayed through the NTS and PBN to forebrain areas such as the hypothalamus, amygdala, thalamus, and insular cortex. The insular cortex has dense reciprocal connections with the ACC, lateral hypothalamic area, NTS, and PBN. These regions are also reciprocally connected. ACC, anterior cingulate cortex; CeA, central amygdala; PBN, parabrachial nucleus; PAG, periaqueductal gray; NA, nucleus ambiguus; DMV, dorsal motor nucleus of the vagus; NTS, nucleus of the solitary tract; VLM, ventrolateral medulla [Mo J, Huang L, Peng J , Ocak U, Zhang J, Zhang JH, 2019].

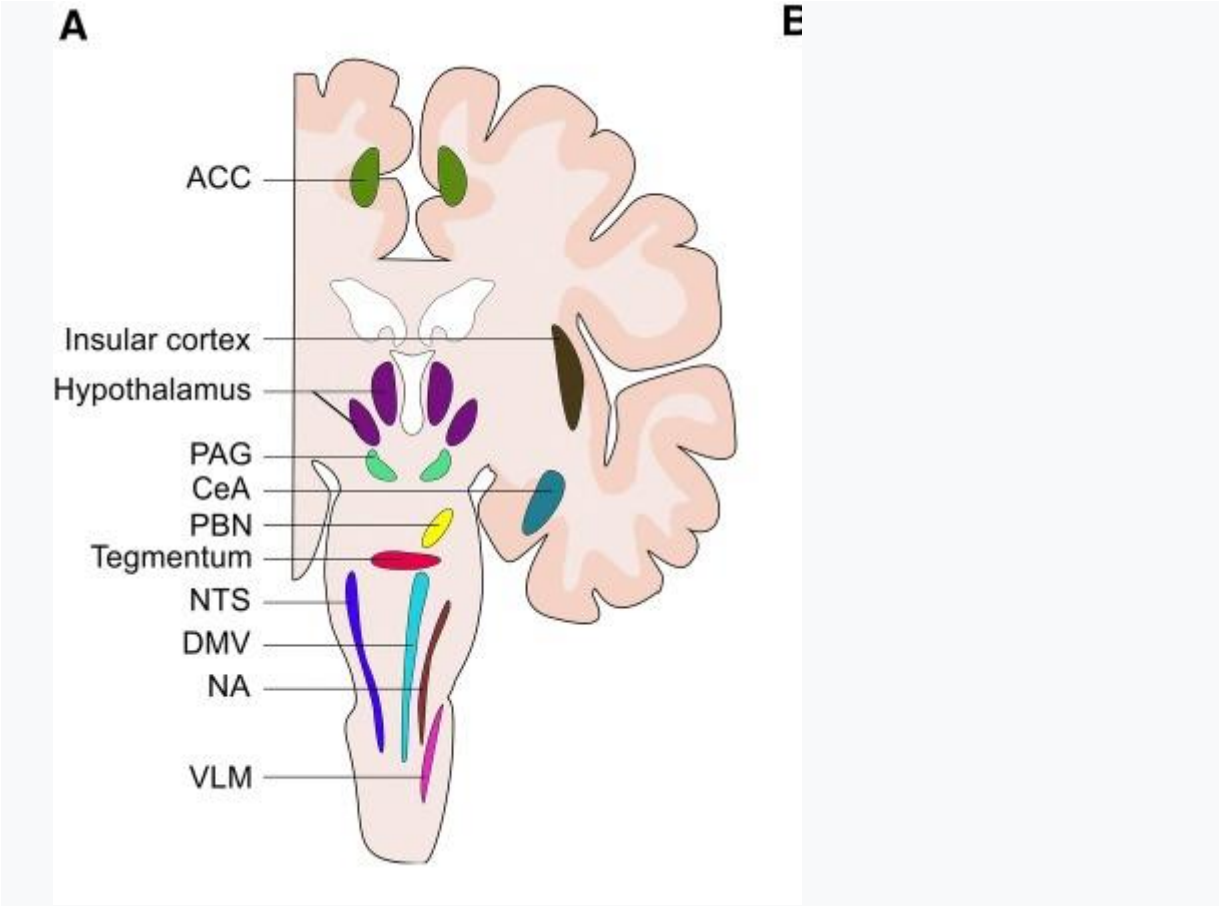


Fig. 20. Brain structures of the central autonomic network
ACC, anterior cingulate cortex; PAG, periaqueductal gray; CeA, central amygdala; PBN, parabrachial nucleus; NTS, nucleus of the solitary tract; DMV, dorsal motor nucleus of the vagus; NA, nucleus ambiguus; VLM, ventrolateral medulla [Mo J, Huang L, Peng J , Ocak U, Zhang J, Zhang JH, 2019].

In this study, increase in heart rate and sympathetic shift of sympatho-vagal balance while decrease in vagally-mediated HRV are combined not with inhibition of prefrontal activity, but with its **drastic increase**. In my opinion, the only rational way out to explain such a blatant paradox can be the assumption of a **paradoxical activation** of the central nucleus of the amygdala, instead of its inhibition.

Standing on the shoulders of quoted **Giants**, I interpret the obtained results as follows. Under the influence of adaptogens (about the mechanism a little later), the activity of the delta-rhythm generating neurons of the medial prefrontal and anterior cingulate cortex, which project to the Fp1, Fp2, F3 and F8 loci, drastical increases. The listed cortical structures have a paradoxal tonic **activating** effect on the central nucleus of the amygdala (CeA). The activation of CeA inhibits the nucleus of the solitary tract (NTS), which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons, and simultaneously inhibits vagal motor neurons in the nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVN). In addition, the CeA directly activate the sympathoexcitatory neurons in the RVLM. The net (ultimate) effect of increased prefrontal activity is the disinhibition of sympathoexcitatory circuits with an increase in heart rate and a decrease in vagal tone (all its HRV markers). Activated RVLM neurons send excitatory projections to preganglionic sympathetic neurons of the intermediolateral (IML) cell columns of the spinal cord. These neurons activate nonadrenergic neurons of the stellate and other paravertebral ganglia, which send axons that contribute to the cardiac plexuses innervating the heart. Parasympathetic output is mediated by vagal neurons located in the

ventrolateral portion of the NA and, to a lesser extent, the DVN. These neurons send preganglionic axons that synapse on cholinergic and noncholinergic neurons located in the cardiac and other ganglia [Palma JE & Benarroch EE, 2014].

In this study, autonomic regulation of the heart plays the role of only a mirror of autonomic regulation as a whole, common to all innervated organs, primarily endocrine and immune, as well as vessels of skin and muscle, sweat glands and abdominal viscera. I will start with the second set as less important. A decrease in diastolic pressure is probably a consequence of the activation of beta-adrenergic vasodilatory innervation vessels of skin and muscle. A decrease in electroconductivity of acupuncture point MC(AVL) Right is probably a consequence of the activation of sympathetic M-cholinnergic innervation of sweat glands of the right hand. When interpreting the detected decrease in the energy of the first Chakra, it should be taken into account that Korotkov KG [2007] put forward the concept that each Chakra is associated with a part of the **finger**. This approach is embodied in the "GDV Chakras" program, which allows us to quantify the state of ***virtual*** Chakras, which, according to our laboratory data, correlates with the electrical conductivity of acupuncture points [Babelyuk VY et al., 2021c]. It is important to note that the state of this Chakra is registered using a polyethylene filter, which excludes the influence of perspiration on the GDI. It is interesting that a one-way leftward shift of symmetry was found for variables of different genesis: theta-rhythm of EEG, electroconductivity of acupuncture point MC(AVL), gas-discharge image and second Chakra. This is consistent with the revealed asymmetry of PSD changes in different loci. Finally, the metabolic effects of adaptogens (decrease in plasma levels of cholesterol, direct bilirubin and C-RP) revealed in this study are also apparently related to changes in sympathetic and vagal regulation of metabolism in the liver (Fig. 21).

It is time to discuss the role of the nervous system in the endocrine and immune effects of adaptogens. To do this, I should once again stand on the shoulders of other **Giants** (Fig. 21).

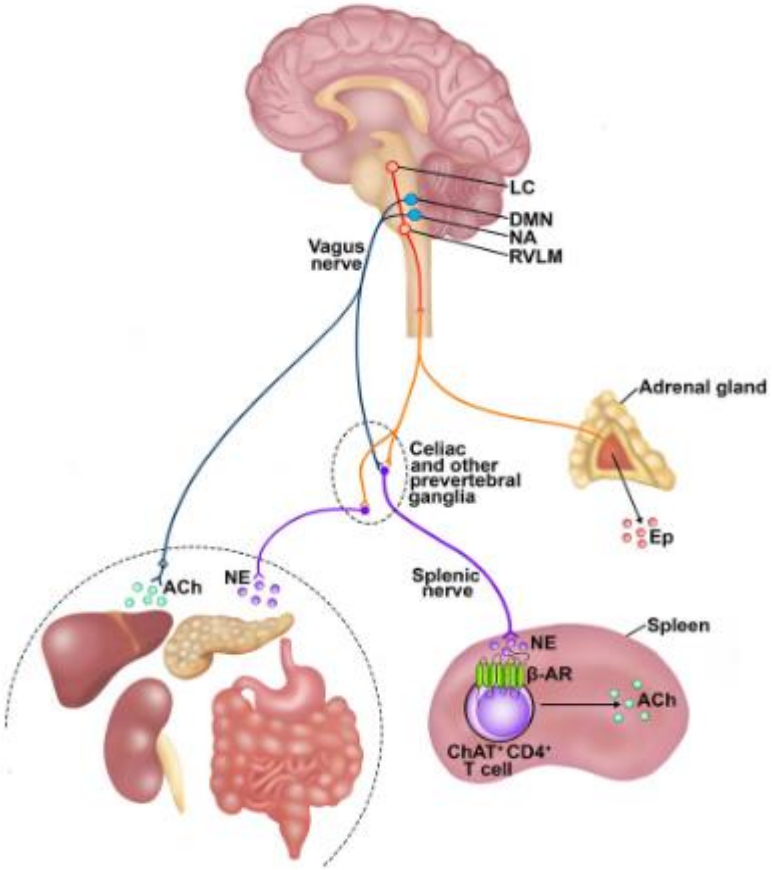


Figure 21. Anatomy of efferent autonomic neurons with a role in immune regulation

Efferent vagus nerve neurons originate in the dorsal motor nucleus of the vagus (DMN), and nucleus ambiguus (NA) in the brainstem medulla oblongata. These preganglionic cholinergic neurons give projections to visceral organs in the thoracic and abdominal cavity, including the lungs, heart, liver, gastrointestinal tract, kidneys and pancreas. They interact with postganglionic vagal neurons in proximity or within the innervated organs, and these neurons release predominantly acetylcholine. Vagus nerve preganglionic neurons also terminate in the celiac ganglia and the superior mesenteric ganglion where the splenic nerve originates. Splenic nerve catecholaminergic neurons release norepinephrine (NE) in spleen. NE interacts with β2-adrenergic receptors on choline acetyltransferase $(ChAT)^{+}CD4^{+}$ T cells and causes release of acetylcholine. The locus coeruleus (LC) and the rostroventrolateral medula (RVLM) are brain regions associated with sympathetic control. RVLM give descending projections to sympathetic neurons in the spinal cord. Sympathetic preganglionic (cholinergic) fibers project to paravertebral (not shown) and prevertebral ganglia, including the celiac ganglia. Postganglionic fibers release predominantly NE in the innervated visceral organs. Postganglionic fibers from paravertebral ganglia innervate the lungs and the heart (not shown). Postganglionic fibers from perivertebral ganglia innervate the, liver, gastrointestinal tract, kidneys, pancreas and other visceral organs. Sympathetic preganglionic fibers also innervate the adrenal medulla and stimulate the secretion of epinephrine (Ep) from chromaffin cells [Chavan SS, Pavlov VA, Tracey KJ, 2017].

As we can see, the sympathotonic effect of adaptogens due to the corresponding neurogenic mechanisms is accompanied by an increase in the plasma levels of catecholamines (marker: 1/Mode HRV), cortisol and calcitonin (for some reason only in women), instead, a decrease in the levels of triiodothyronine and testosterone (also only in women). This is combined with the lowering of the energy of the first Chakra. I will repeat that the first Chakra is related to the testicles or adrenals (which are a source of testosterone in women). ***A wonderful reconciliation of Western and Eastern paradigms, isn't it?***

Figure 21 perfectly illustrates the neurogenic mechanism of the reduction in the level of IL-1 in the blood revealed in this study by inhibiting its synthesis by macrophages of the spleen

through the mediation of α7N-cholinergic receptors in the course of the famous “cholinergic anti-inflammatory reflex (pathway)” [Tracey KJ, 2002; 2007; 2009; 2010].

The apotheosis of the above I consider Tracey's KJ [2007] concept of "immunological homunculus". According to the author, there is a structured, somatotopically organized neural network that controls the specific components of the immune response through the connection of the input and output. Such a theoretical organization is similar to the classic homunculus, which demonstrates that specific areas of the brain control the specific parts of the body, and in the future it will be possible to construct an "immunological homunculus". For example, one region of the brain can control cytokine responses in the liver, and the other - the activation of T cells in the spleen or lymph nodes. Certain centers can integrate information about the presentation of antigens, while others are about the process of maturation of dendritic cells. Separate neurological domains in the central nervous system may regulate the state of general readiness of the innate immunity to respond to pathogens or injury. The existence of neuroanatomical maps of cholinergic anti-inflammatory reflex is a significant step towards the identification of other domains in the immunological homunculus, which is crucial for maximizing body protection and maintaining health during immune responses.

However, in subsequent works of this laboratory [Pavlov VA & Tracey KJ, 2012; Chavan SS & Tracey KJ, 2017; Chavan SS et al., 2017], this hypothesis was not developed. And only in 2018, the mention of him appeared in their review [Pavlov VA et al., 2018], but, unfortunately, without specification.

I draw attention to the fact that the author's scheme (Fig. 22) at the end of each signature is a question mark (?), that is, it is not a statement, but a hypothesis.

Under the influence of this hypothesis our laboratory carried out research for its verification [Kul’chyns’kyi AB et al., 2016; 2017; 2017a; 2017b; Popovych.IL et al., 2017; 2018; Mel’nyk OI et al., 2019].

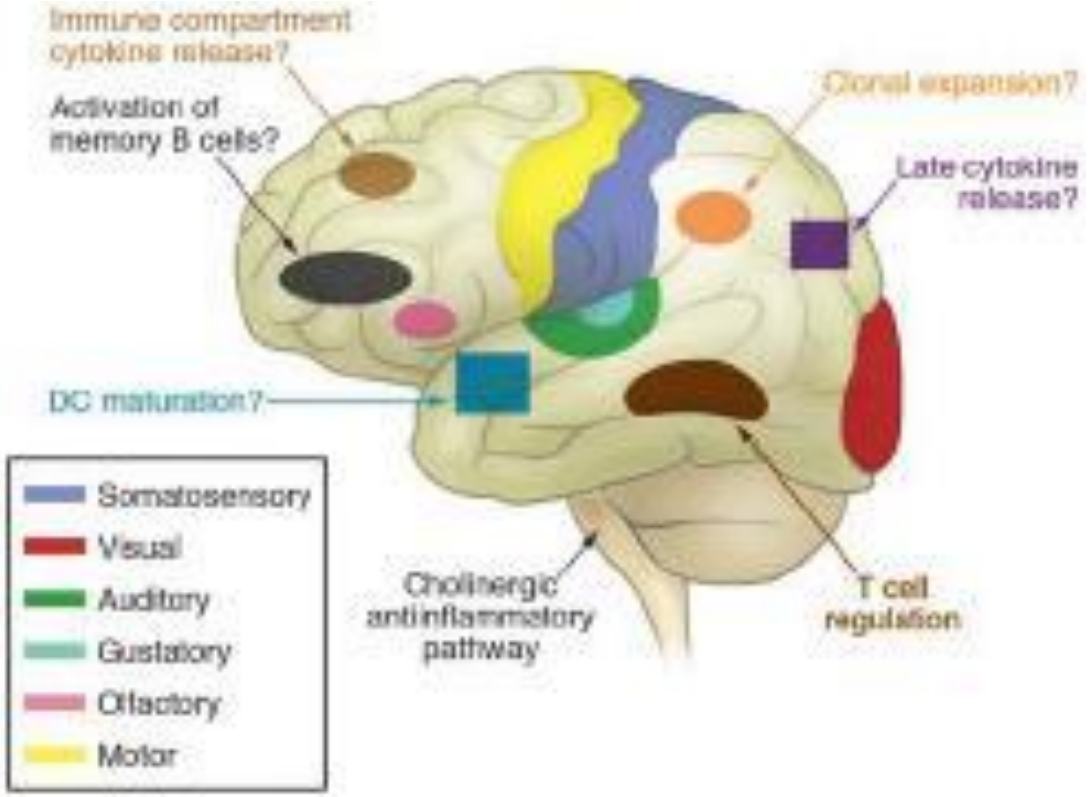


Fig. 22. Scheme of immunological homunculus [Tracey KJ, 2007]

How do the results obtained in this study fit into the concept/hypothesis of immunological homunculus? As can be seen in the comparative Table 22, in the putative cortical **center of activation of memory B cells**, inhibition of the activity of θ-rhythm generating neurons is accompanied by a decrease in the blood levels of immunoglobulins M and A. The **center of late cytokine release**, by Tracey KJ, is projected between parietal and occipital loci. This is consistent with our data on the association of a decrease in the levels of IL-1 as well as C-reactive protein with the inhibition of β-rhythm generating neurons in loci O2 and P4 while activation localized there of δ-rhythm generating neurons. If we assume that the cortical **center of regulation of T-lymphocytes** is projected onto the T6 locus, then it turns out that it exerts an inhibitory effect on the blood level of T-regulatory and T-cytolityc lymphocytes. At the same time, our data give reason to propose an alternative hypothesis about upregulation of T-lymphocytes by δ- and α-rhythm generating neurons that project to prefrontal loci. Finally, my modest contribution to the concept of immunological homunculus is the hypothesis of localization in the right occipital cortex of δ-rhythm generating neurons responsible for the **regulation of phagocytosis**.

Table 22. Agreed and different propositions of of immunological homunculus

EEG and Immune Variables	EEG and Immune response	EEG and Immune Variables	EEG and Immune response
Tracey's hypothesis		Tracey's hypothesis	
Activation of memory B cells		Late cytokine release	
Fp2-θ PSDr	-0,26±0,12	P4-δ PSDr	+0,34±0,17
IgM	-0,39±0,22	P4-β PSDr	-0,34±0,12
IgA	-0,24±0,14	O2-β PSDr	-0,33±0,13
		Interleukin-1	-0,42±0,27
		C-reactive Protein	-0,26±0,06
Tracey's hypothesis		Popovych's hypothesis	
T cells regulation		T cells regulation?	
T6-β PSDr	-0,25±0,12	Fp2-δ PSDa	+3,13±1,56
$CD3^+CD25^+$ T-regulatory Lym	+0,51±0,19	Fp1-δ PSDa	+3,14±1,59
$CD3^+CD8^+$ T-cytolytic Lymph	+0,60±0,26	F3-δ PSDa	+2,53±1,34
Popovych's hypothesis		F8-δ PSDa	+7,62±3,11
Activation of Phagocytosis?		F7-α PSDr	+0,29±0,12
O2-δ PSDr	+0,42±0,17	F8 PSD Entropy	-0,46±0,21
Microbial Count vs E. coli	+0,40±0,17	$CD3^+CD25^+$T-regulatory	+0,51±0,19
Microbial Count vs St. aureus	+0,39±0,13	$CD3^+CD8^+$T-cytolytic	+0,60±0,26
Killing Index vs Staph. aureus	+0,79±0,20		
Killing Index vs E. coli	+0,65±0,12		
Bactericidity vs E. coli	+1,64±0,39		
Bactericidity vs Staph. aureus	+1,54±0,42		
CIC	+0,43±0,13		

It is time to return to finding out how adaptogens, which are different in nature and place of application, have the same effects on the body? The answer is in the wonderful drawing of **Giants**!

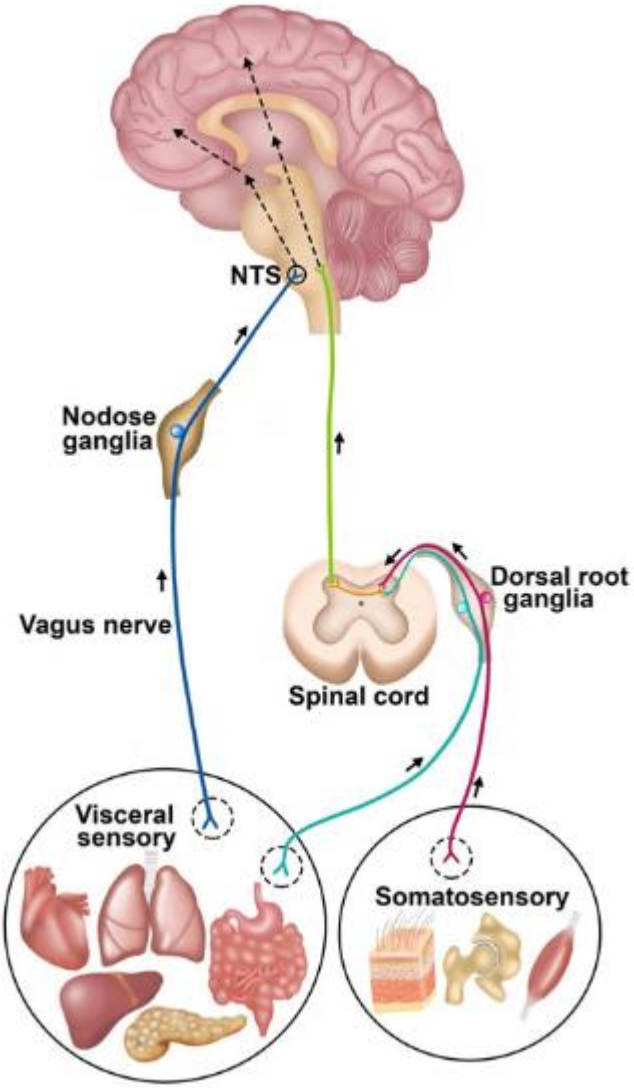


Figure 23. Anatomy of sensory neurons with a role in neuro-immune interaction
Sensory neurons with cell bodies in the dorsal root ganglia are somatosensory and visceral. Somatosensory neurons, innervating the skin, joints and muscles, and visceral neurons, innervating the gastrointestinal track, pancreas, liver, lungs, heart and other organs enter the spinal cord via the dorsal horn. In the spinal cord central axonal terminals of these neurons make synaptic contacts with interneurons and relay neurons transmitting the signals to the brainstem and other brain areas. Vagus sensory neurons originate in the nodose ganglia (anatomically divided into nodose and jugular ganglia in rats and humans) and innervate visceral organs, including gastrointestinal tract, pancreas, liver, lungs, heart and other organs. Most of their central axons terminate in the nucleus tractus solitarius (NTS), with projections to other brainstem and forebrain areas. The activity of somatosensory and visceral neurons communicating peripheral information to the CNS is altered in inflammatory and autoimmune conditions affecting the innervated areas in visceral and somatic organs and tissues [Chavan SS, Pavlov VA, Tracey KJ, 2017].

Let me remind you that the electrodes of the electrostimulation device are applied to the palms. A major class of somatosensory neurons are nociceptors, preferentially sensitive to noxious stimuli, including heat and mechanical stimulation or to a stimulus that would become noxious if prolonged [Dubin AF & Patapoutian A, 2010]. In this case, electrical stimulation of the skin of the palms is not accompanied by unpleasant sensations, especially painful ones. Impulses from somatosensory neurons through a series of switches reach the neurons of the CNS, or rather the central autonomic network.

The receptor field of another adaptogen – Naftussya bioactive water – is gut mucosa, especially the small intestine. Many years of research in our laboratory have proven that the biological activity of Naftussya water is determined by organic substances (in particular, agonists of aryl hydrocarbon receptors) and autochthonous microflora [Ivassivka SV et al., 1990; 2010; Ivassivka SV, 1997; Dats'ko OR et al., 2008; Bilas VR & Popovych IL, 2009; Popovych IL & Ivassivka SV, 2009; Popovych AI, 2018; 2019; Popovych IL et al., 2018; 2022; Zukow W et al., 2020].

Based on physiological responsiveness, vagal afferents can be grouped in mechanosensitive fibers and chemical-sensitive afferents activated by a variety of **chemical stimuli** [Mazzone SB & Undem BJ, 2016], which in our case are organic substances.

Vagal afferent neurons, innervating the gastrointestinal tract are in position to detect gastrointestinal pathogens, including Campylobacter jejuni and signal the brain. Oral inoculation with C. jejuni results in increased c-Fos immunoreactivity in vagal sensory ganglia and in timely-dependent manner in the NTS and other brainstem and forebrain regions, including area postrema, the ventrolateral medulla, locus coeruleus, thalamus, different hypothalamic nuclei, amygdala, and insular cortex (Fig. 18). This neuronal activation occurs in the absence of increased circulating levels of pro-inflammatory cytokines, including TNF and IL-1β. Although the mechanisms of the pathogen-sensory neuron interactions leading to neuronal activation remain to be elucidated these findings establish vagal sensory neurons as a pathway for early signaling of gut infection to the brain [Lai NY et al., 2017; Goehler LE et al., 2005]. Activation of vagal afferents by bacterial products is mediated by TL-4 receptors expressed on these neurons, or via chemosensory cells in the associated vagal paraganglia [Hosoi T et al., 2005; Goehler LE et al., 2000; Goehler LE et al., 1999].

The above provides grounds for the assumption that the autochthonous microflora of Naftussya bioactive water acts in a similar way.

Figs. 23 and 18 illustrates that irritation from Naftussya water factors can also be transmitted through sympathetic afferents to dorsal root ganglia. Spinal afferents relay on second-order neurons of lamina I, which project to the thalamus, PAG, and othe brainstem and hypothalamic targets.

In addition, activation of peripheral axon terminals of receptors of both skin and gut causes the release of **calcitonin** gene-related peptide (CGRP), substance P (SP), vasoactive intestinal peptide (VIP) and other neuropeptides. These substances act via their cognate receptors on immune cells and vasculature and promote or suppress inflammation [Pinho-Ribeiro FA et al., 2017]. For instance, the release of SP, CGRP and VIP from spinal nociceptors innervating the gastrointestinal tract have been shown to have protective or deleterious effects in the regulation of colonic inflammation [Lai NY et al., 2017]. The immune cell-sensory neuron interplay may occur via axon reflex mechanisms.

Therefore, both the electric current applied to the skin of the palms and the chemical and bacterial (antigenic) factors of Naftussya bioactive water applied to the mucose of the digestive tract eventually change the activity of the nervous structures of the central autonomic network, which, in turn, modulate the state of the endocrine and immune systems and metabolism. This conclusion fits into the concept of the neuro-endocrine-immune complex [Popovych IL, 2009] and the functional-metabolic continuum [Gozhenko AI, 2016].

I consider it necessary to repeat that such a conclusion is still simplified, since immunocytes, through their cytokines and hormones, are also able to modulate the activity of neurons and endocrinocytes [Korneva EA et al., 1993; Korneva EA, 2020; Khaitov RM, 2005; Sternberg EM, 2006; Nance DM & Sanders VM, 2007; Uchakin PN et al., 2007; Popovych IL, 2009; Thayer JF & Sternberg EM, 2009; 2010].

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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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