

Neurotropic effects of distilled water administered to recipients under the guise of exposure to Kyokushin karate katas

VALERIY E. BABELYUK¹, IGOR L. POPOVYCH², WALERY ZUKOW³

^{1,2} Ukrainian Scientific Research Institute of Medicine of Transport, Odesa, UKRAINE

² Bohomolets' Institute of Physiology of NAS, Kyiv, UKRAINE

³ Nicolaus Copernicus University, Torun, POLAND

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Abstract

Background. This article introduces the project "Functional information: Neurotropic effects of water exposed to informational factors." The first informational factor used was a placebo, specifically distilled water with verbal suggestion. Subsequent factors included ordinary water exposed to Kyokushin karate katas, Sense and Cross fields, Christian prayer, and Holy water. Additionally, water exposed to a magnetic field and bioactive Naftussya water from Truskavets' Spa were used. **Material and methods.** The study involved five male participants (aged 26–60 years, right-handed, without clinical diagnoses). In the morning, under baseline conditions, ECG recordings were taken to assess heart rate variability (HRV) parameters, alongside quantitative EEG measurements at 16 loci. Then, participants drank 50 ml of distilled water with the false message that this water had been treated (exposed to kyokushin karate katas) by the first author known as a karate practitioner, hypnotist and psychotherapist. After 1.5 hours, repeated testing was performed. The next day, a control experiment was conducted with the same distilled water, and earlier - with water from a well and pipe. In addition, the data of the baseline of the same participants, obtained both before and after the main experiment, were used. **Results.** Preliminary data analysis revealed that the effects of distilled, well, and tap waters did not differ significantly, so they were combined into one group (Control Waters, CWs). It was found that 1.5 hours after the consumption of CWs, 17 variables deviated significantly from the initial levels, and another 10 were slightly but statistically significant. We interpreted them as spontaneous rhythmic changes, but not the effects of water as such. Taking spontaneous rhythmic changes into account, an essential (per se) enhancing neurotropic Placebo effect ($Z \pm SD$) was found on 9 variables (0.92 ± 0.66), a weak inhibitory effect on 8 variables (-0.23 ± 0.06), a moderate inhibitory effect on 10 variables (-0.67 ± 0.15), and a noticeable inhibitory effect on 9 variables (-1.14 ± 0.27). Significant individual differences in neurotropic reactions to placebo were revealed. **Conclusion.** Placebo as a carrier of functional information exerts pronounced modulating, mainly inhibitory, neurotropic effects. The neurotropic effects of other informational factors will be demonstrated in subsequent publications.

Keywords: placebo, distilled water, spontaneous rhythmic changes, EEG, HRV, men.

Introduction

If we translate the first lines of the *Gospel of John* from religious language to scientific language (logos = word = Information; God = World Mind = Information space of the Universe), we get: "The first was **Information**, and the World Mind had **Information**, and the World Mind was **Information**. It was primary in the World Mind ... Everything arose through **Information** ... **Information** became a body." By the way, here is the answer to the main question of philosophy regarding the primacy of the ideal or the material.

Sayood (2018) stated that the last couple of decades has seen both a revival of interest, and a more firmly grounded, experimentally justified use of **information** theory. We can view cognition as the process of transforming perceptions into information where we use information in the colloquial sense of the word. The author described applications of information theory across a range of cognition research, from neural coding to cognitive control and **predictive** coding.

Biological information encoded in genomes is fundamentally different from and effectively orthogonal to Shannon's **entropy**. The biologically relevant concept of information has to do with 'meaning', i.e. encoding various biological functions with various degree of evolutionary conservation. Information encoded in genomes is defined vertically but not horizontally (Koonin, 2016).

According to Adami (2016), information is a precise concept that can be defined mathematically, but its relationship to what we call 'knowledge' is not always made clear. Furthermore, the concepts 'entropy' and 'information', while deeply related, are distinct and must be used with care, something that is not always achieved in the literature. In this elementary introduction, the concepts of entropy and information are laid out one by one, explained intuitively, but defined rigorously. Information is that which allows you (who is in

possession of that information) to make **predictions** with accuracy better than chance. We all understand that information is useful. The author argued that, when you thought that the information you were given was not useful, then what you were exposed to was most likely not information. That stuff, instead, was mostly entropy (with a little bit of information thrown in here or there). Entropy is just a word we use to quantify how much is not known. Information is 'unconditional entropy minus conditional entropy'.

Obviously, **placebo** is one of the bright **informational factors**.

Glossary. Placebo: Latin term for "I shall please". Used to indicate sham treatments or inert substances such as sugar pills or saline infusions. **Placebo effects:** Defined as any improvements in a symptom or physiological condition of individuals following a placebo treatment. There are different mechanisms underlying this phenomenon, including spontaneous remission, regression to the mean, natural course of a disease, biases and placebo responses. **Placebo responses:** The outcomes caused by a placebo manipulation. The placebo response reflects the neurobiological and psycho-physiological response of an individual to an inert substance or sham treatment and is mediated by various factors that make up the treatment context. Importantly, placebo responses are not restricted to placebo treatments and can also modulate the outcome of any active treatment (Enck et al., 2013). The use of placebo in clinical practice has been the topic of extensive debate in the bioethics literature, with much scholarship focusing on concerns regarding deception. While considerations of placebo without deception have largely centred on open-label placebo, this paper considers a different kind of ethical quandary regarding placebo without an intent to deceive - one where the provider believes a treatment is effective due to a direct physiological mechanism, even though that belief may not be supported by rigorous scientific evidence (Kalokairinou et al., 2022).

Open-label placebos (OLPs) are placebos without deception in the sense that patients know that they are receiving a placebo. Von Wernsdorff et al. (2021) carried out the systematic review and analyze the effect of OLPs in comparison to no treatment in clinical trials. Randomized controlled trials of any medical condition or mental disorder comparing OLPs to no treatment were included. 1246 records were screened and thirteen studies were included into the systematic review. Eleven trials were eligible for meta-analysis. These trials assessed effects of OLPs on back pain, cancer-related fatigue, attention deficit hyperactivity disorder, allergic rhinitis, major depression, irritable bowel syndrome and menopausal hot flushes. Risk of bias was moderate among all studies. Authors found a significant overall effect (standardized mean difference = 0.72; 95% CI 0.39-1.05; $p < 10^{-4}$, $I^2 = 76\%$) of OLP. Thus, OLPs appear to be a promising treatment in different conditions but the respective research is in its infancy. Authors concluded that more research is needed, especially with respect to different medical and mental disorders and instructions accompanying the OLP administration as well as the role of expectations and mindsets. This article starts the project "Functional Information. Neurotropic effects of water exposed to informational factors". As the first informational factor, a placebo was used, in particular, distilled water with a verbal suggestion. The following informational factors served as ordinary water exposed to: Kyokushin karate katas, Sense and Cross fields, Christian prayer as well as Holy water. On the other hand, water exposed to the material factor such as magnetic fields as well as bioactive Naftussya water of Truskavets' Spa was used.

Research Aim. To investigate the neurotropic effects of distilled water given to recipients under the guise of being exposed to kyokushin karate katas, by analyzing EEG and HRV parameters in healthy male subjects.

Research Problems.

1. What are the measurable neurotropic effects of distilled water presented as exposed to kyokushin karate katas compared to baseline and control water consumption?
2. Can these effects be distinguished from spontaneous rhythmic changes occurring over time?
3. Which EEG and HRV parameters are most susceptible to modulation by this placebo intervention?
4. Are there correlations between individual differences in baseline physiology and the placebo response?
5. How does the suggestion related to kyokushin karate katas influence the neurotropic effects of distilled water?

Research Hypotheses.

1. Distilled water given under the guise of exposure to kyokushin karate katas will produce measurable neurotropic effects compared to baseline and control water consumption.
2. These effects will be distinguishable from spontaneous rhythmic changes that occur over time.
3. The intervention will modulate specific EEG and HRV parameters, particularly those related to autonomic nervous system activity.
4. The magnitude and direction of effects will correlate with individual differences in baseline physiology and personality traits.
5. Neurotropic effects will involve both enhancement and inhibition of different neurophysiological parameters.
6. The effects will be detectable using discriminant analysis of EEG and HRV data.
7. Identifiable patterns or clusters of neurophysiological changes associated with the intervention will be observed.
8. The suggestion related to kyokushin karate katas will elicit specific changes in EEG and HRV parameters, differing from the effects of ordinary distilled water.

Material and methods

Participants. The object of physiological observation were 5 men (aged 26, 35, 52, 54 and 60 years, right-handed, without a clinical diagnosis), including the second author PhD Po. First of all, volunteers filled a questionnaire with the purpose of estimation of level of the trait anxiety by STAI of Spielberg (1983) in modification of Khanin (Practical ..., 1998).

Procedure / Test protocol / Skill test trial / Measure / Instruments.

In the morning (November 17, 2010), under basal conditions, recorded an electrocardiogram in II lead for 7 minutes in the sitting position to assess the parameters of heart rate variability (HRV) (software and hardware complex "CardioLab+HRV" produced by "KhAI-MEDICA", Kharkiv, Ukraine). For further analyses the following HRV parameters were selected. Temporal parameters (Time Domain Methods): HR, the mode (Mo), the standard 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 than 50 msec (pNN_{50}); triangular index (TNN). Spectral parameters (Frequency Domain Methods): absolute (msec^2) and relative (%) power spectral density (PSD) bands of HRV: high-frequency (HF, range $0.4\div0.15$ Hz), low-frequency (LF, range $0.15\div0.04$ Hz), very low-frequency (VLF, range $0.04\div0.015$ Hz), and ultralow-frequency (ULF, range $0.015\div0.003$ Hz). Calculated classical indexes: LF/HF; $(\text{VLF}+\text{LF})/\text{HF}$; $\text{LFnu}=100\%\cdot\text{LF}/(\text{LF}+\text{HF})$ (HRV, 1996; Berntson et al., 1997; Baevsky & Ivanov, 2001; Baevsky & Chernikova, 2017). Then we quantitative EEG recorded at rest 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. Two minutes after the eyes had been closed, 25 sec of artifact free EEG data were collected by computer. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute ($\mu\text{V}^2/\text{Hz}$) and relative (%) PSD of basic rhythms: β ($35\div13$ Hz), α ($13\div8$ Hz), θ ($8\div4$ Hz) and δ ($4\div0.5$ Hz) in all loci, according to the instructions of the device. In addition, we calculated coefficient of Asymmetry (As) and Laterality Index (LI) for PSD each Rhythm using equations (Newberg, 2001):

As, % = $100\cdot(\text{Max} - \text{Min})/\text{Min}$; LI, % = $\Sigma [200\cdot(\text{Right} - \text{Left})/(\text{Right} + \text{Left})]/8$ (Newberg et al., 2001).

We calculated also for HRV and each locus of EEG the Entropy (h) of normalized PSD using Popovych's (Popadynets et al., 2020; Gozhenko et al., 2021) equations based on classic Shannon's (1948) equation:

$h_{\text{EEG}} = - [\text{PSD}\alpha\cdot\log_2 \text{PSD}\alpha + \text{PSD}\beta\cdot\log_2 \text{PSD}\beta + \text{PSD}\theta\cdot\log_2 \text{PSD}\theta + \text{PSD}\delta\cdot\log_2 \text{PSD}\delta] / \log_2 4$;

$h_{\text{HRV}} = - [\text{PSDHF}\cdot\log_2 \text{PSDHF} + \text{PSDLF}\cdot\log_2 \text{PSDLF} + \text{PSDVLF}\cdot\log_2 \text{PSDVLF} + \text{PSDULF}\cdot\log_2 \text{PSDULF}] / \log_2 4$.

4. After completing the initial testing, participants drank 30 ml of distilled water at room temperature with the *false message* that this water had been treated (exposed to Kyokushin karate *katas*) by the first author. The first author has long been known to the participants of the experiment as a karate practitioner, hypnotist and PhD psychotherapist, that is, in this case, distilled water was a classic placebo (will henceforth be nominated as Tested Water). After 1.5 hours (89 ± 16 minutes), repeated testing was performed.

The next day (November 18), a control experiment was conducted with the same distilled water, and earlier - with water from a well (November 15) and water pipe passed through a purification filter (November 10). In addition, the data of the primary testing (baseline) of the same participants, conducted both before (November 16, 12, 11, 09, 08, October 22, 20, 10) and after (November 19) the main experiment, were used.

Data collection and analysis / Statistical analysis.

Statistical processing was performed using a software package "Microsoft Excell" and "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA).

Descriptive Statistics. 1. Measures of central tendency. Arithmetic mean (Mean). Mode (Mo) for HRV parameters.

2. Measures of dispersion. Standard deviation (SD). Standard error of the mean (SE).

3. Coefficients of variation. Coefficient of variation (Cv) for some parameters.

Inferential Statistical Methods.

1. Data normalization. Variables were normalized using the formula: $Z = 4\cdot(V - N)/(\text{Max} - \text{Min}) = (V - N)/\text{SD} = (V/N - 1)/\text{Cv}$, where V is the actual value, N is the reference value, SD is the standard deviation, and Cv is the coefficient of variation.

2. Discriminant analysis. Stepwise discriminant analysis was used to select variables that best differentiate between groups. Coefficients of discriminant functions and classification constants were calculated. Wilks' Lambda statistic was used to assess the significance of discriminant functions. F-test was conducted to evaluate the significance of individual variables in the model. Mahalanobis distances squared between groups were calculated.

3. Correlation analysis. Correlation coefficients between EEG and HRV variables were calculated. A formula was applied to calculate critical values of the correlation coefficient: $|r| = \{\exp[2t/(n-1.5)^{0.5}] - 1\} / \{\exp[2t/(n-1.5)^{0.5}] + 1\}$

4. Canonical correlation analysis. Canonical correlation analysis was performed between EEG and HRV parameters. Canonical correlation coefficients (R) and their squares (R^2) were calculated. Chi-square test was used to assess the significance of canonical correlations.

5. Cluster analysis. Cluster analysis was applied to group variables with similar characteristics.

6. Significance tests. P-values were used to assess the statistical significance of results. Significance levels were set at: $p < 0.05$, $p < 0.01$, $p < 0.001$.
7. Data visualization. Scatter plots were used to visualize results of discriminant analysis and canonical correlations. Bar graphs were used to present normalized values of variables.
8. Effect analysis. Placebo effects were calculated as the difference between the effects of test water and spontaneous rhythmic changes. These methods allowed for a comprehensive analysis of the data, enabling the assessment of neurotropic effects of the placebo intervention, comparison with baseline and control conditions, and examination of relationships between various neurophysiological parameters.

Results

Preliminary data analysis revealed that the effects of Control Waters (distilled, well, tap water filtered) did not differ significantly, so they were further combined into one group. Adhering to the Truskavetsian Scientific School's analytical algorithm, in order to correctly compare variables expressed in different units and with different variability, the actual/raw parameters were normalized by recalculation by the equations: $Z = 4 \cdot (V - N) / (\text{Max} - \text{Min}) = (V - N) / \text{SD} = (V/N - 1) / \text{Cv}$, where V is the actual value; N is the normal (reference) value; SD and Cv are the standard deviation and coefficient of variation respectively (Polovynko et al., 2016; Popovych et al., 2022). Reference values are taken from the database of the Truskavetsian Scientific School of Balneology (EEG) and instruction (HRV). As a result of the screening of the registered EEG and HRV parameters, those for which **Tested Water** significantly differs from **Baseline** and/or **Control Waters** were selected (Fig. 1).

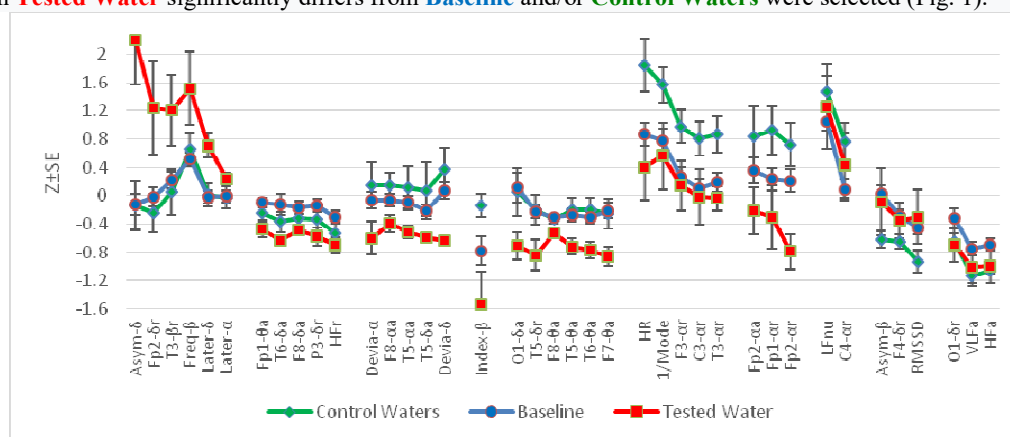


Fig. 1. Patterns of normalized EEG and HRV variables before (Baseline) and 1.5 h after consumption of 30 ml of Control Waters and distilled water falsely told to recipients that it was treated by the author (Tested Water). See please Table 5

Further, the patterns were condensed into 10 clusters, and effects of CWs and essential effects of placebo were also calculated (Fig. 2, details later). At first glance, one gets the impression that after using CWs, only 12 EEG&HRV parameters, condensed in the first and fifth clusters, remain without significant changes, on the other hand, most of the parameters deviate significantly from the basal levels to one degree or another. Secondly, the placebo had an enhancing effect only on 9 EEG&HRV parameters condensed in the first and ninth clusters, on 3 parameters of the tenth cluster the placebo had no effect, instead on 22 parameters it had inhibitory effects of varying severity.

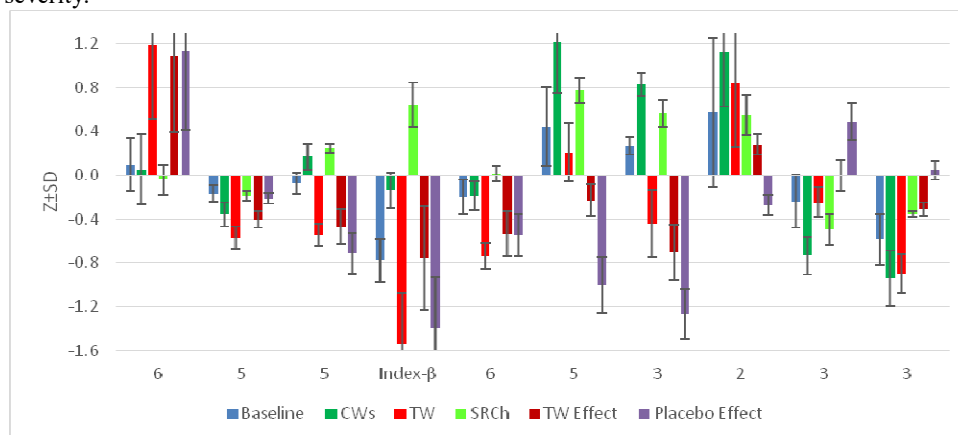


Fig. 2. Clusters of normalized EEG and HRV variables before (Baseline) and 1.5 h after consumption of 30 ml of Control Waters (CWs) and distilled water falsely told to recipients that it was treated by the author (Tested Water, TW). See please Table 5.

Calculated effects of CWs (as spontaneous rhythmic changes, **SRCh** = **CWs** - **Baseline**) and essential effects of placebo (**Placebo Effect** = **TW** - **SRCh**). The number of variables is indicated under each pattern

More on this later, but now let's focus on the results of the discriminant analysis (Klecka, 1989). First of all, it was found that only 28 variables (Tables 1 and 2) were selected by the forward stepwise program as distinguishing ones, i.e. according to the constellation of which the neural states of the participants in the basal period and 1.5 hours after the use of CWs or TW differ significantly from each other.

Table 1. Discriminant Function Analysis Summary for EEG&HRV Variables, their levels (Mean±SE) as well as Reference levels and Coefficients of Variability or SD

Step 28, N of vars in model: 28; Grouping: 3 grs; Wilks' Λ : 0,2189; approx. $F_{(56,1)}=2,8$; $p<10^{-6}$

Variables currently in the model	Groups (n)			Parameters of Wilk's Statistics					Reference (112)	Cv or SD
	Control Waters (15)	Base-line (80)	Tested Water B-P+(5)	Wilks' Λ	Parti-al Λ	F-re-move (2.70)	p-level	Tolerance		
Asymmetry- δ , %	38.3 8.6	38.5 3.7	95.4 16	0.255	0.860	5.69	0.005	0.549	41.8 2.3	0.580
Laterality- δ , %	3.1 6.8	1.6 3.8	30.8 7.0	0.243	0.902	3.81	0.027	0.260	2.5 3.8	SD 39.8
Deviation- δ , Hz	0.77 0.08	0.69 0.03	0.50 0.00	0.232	0.942	2.16	0.123	0.731	0.67 0.03	0.395
Fp2- δ PSD, %	22.0 4.9	26.1 2.5	49.0 12.0	0.236	0.928	2.73	0.072	0.330	26.5 1.7	0.687
F4- δ PSD, %	18.5 2.0	25.6 1.8	24.4 5.0	0.228	0.958	1.52	0.225	0.232	31.2 1.3	0.624
F8- δ PSD, $\mu V^2/Hz$	43 18	66 14	20 10	0.228	0.962	1.38	0.259	0.248	92 14	1.642
T6- δ PSD, $\mu V^2/Hz$	44 11	63 12	22 6	0.242	0.904	3.73	0.029	0.291	74 8	1.110
T5- δ PSD, $\mu V^2/Hz$	97 50	62 10	15 7	0.240	0.912	3.37	0.040	0.163	89 12	1.412
T5- δ PSD, %	22.7 3.9	22.0 1.7	10.9 4.0	0.239	0.917	3.18	0.048	0.130	26.3 1.8	0.696
P3- δ PSD, %	19.6 3.4	23.1 1.5	15.2 2.4	0.230	0.952	1.75	0.181	0.182	25.6 1.7	0.694
O1- δ PSD, %	13.5 1.8	18.7 1.9	12.8 3.5	0.220	0.997	0.12	0.886	0.161	23.5 1.5	0.655
Laterality- α , %	-2.2 5.4	-1.6 2.7	6.7 3.3	0.228	0.961	1.44	0.245	0.322	-1.2 3.2	SD 34.2
Deviation- α , Hz	1.10 0.18	0.98 0.06	0.70 0.12	0.243	0.901	3.86	0.026	0.519	1.02 0.05	0.527
Fp2- α PSD, $\mu V^2/Hz$	146 32	111 13	68 24	0.258	0.850	6.17	0.003	0.051	84 7	0.867
F8- α PSD, $\mu V^2/Hz$	49 9	38 4	22 6	0.235	0.932	2.56	0.085	0.146	42 5	1.202
C4- α PSD, %	46.3 4.0	36.2 2.2	41.2 7.0	0.306	0.714	14.0	10 ⁻⁵	0.040	34.8 1.4	0.432
F3- α PSD, %	48.8 3.7	37.4 2.2	35.4 5.5	0.245	0.894	4.16	0.020	0.026	33.2 1.5	0.479
C3- α PSD, %	48.8 3.9	37.1 2.2	35.1 6.5	0.241	0.909	3.51	0.035	0.028	35.4 1.6	0.468
T5- α PSD, $\mu V^2/Hz$	146 48	112 15	48 15	0.234	0.934	2.48	0.091	0.137	128 15	1.242
Asymmetry- β , %	13.5 1.9	23.8 1.9	22.0 7.5	0.258	0.848	6.27	0.003	0.589	23.4 1.5	0.679
Index- β , %	92.3 1.8	85.1 2.3	76.4 5.3	0.233	0.939	2.27	0.111	0.539	93.9 1.1	0.121
Frequency- β , Hz	20.8 1.0	20.2 0.4	24.6 2.3	0.239	0.917	3.18	0.048	0.533	17.9 0.4	0.244
Fp1-0 PSD, $\mu V^2/Hz$	18.3 2.7	21.6 1.6	12.8 2.8	0.253	0.864	5.51	0.006	0.290	23.9 2.2	0.987
Heart Rate, bpm	85.4 3.0	77.3 1.4	73.4 5.1	0.233	0.940	2.25	0.113	0.021	69.9 0.9	0.120
Mode HRV, msec	699 26	780 17	800 59	0.229	0.954	1.68	0.193	0.021	858 9	0,117
PSD VLF, msec ²	483 86	708 60	450 164	0.232	0.944	2.06	0.135	0.217	1400 78	0,588
PSD HF, msec ²	114 20	176 14	95 34	0.222	0.984	0.55	0.579	0.201	407 27	0.706
PSD HF, %	9.0 1.0	10.8 0.6	7.3 1.0	0.241	0.910	3.47	0.036	0.335	14.5 0.9	0.676

Table 2. Summary of forward stepwise analysis. Variables ranked by criterion Δ

Variables currently in the model	F to enter	p-level	Δ	F-value	p-level
Asymmetry- δ , %	7,36	0,001	0,868	7,36	10^{-6}
C4- α PSD, %	2,93	0,058	0,818	5,06	10^{-6}
C3- α PSD, %	4,75	0,011	0,744	5,05	10^{-6}
Deviation- α , Hz	4,41	0,015	0,680	5,00	10^{-6}
T5- δ PSD, %	5,11	0,008	0,613	5,16	10^{-6}
Fp1- θ PSD, $\mu V^2/Hz$	3,88	0,024	0,565	5,06	10^{-6}
Asymmetry- β , %	3,09	0,050	0,529	4,87	10^{-6}
PSD HF, msec ²	3,20	0,046	0,494	4,76	10^{-6}
Fp2- δ PSD, %	3,00	0,055	0,463	4,65	10^{-6}
F8- α PSD, $\mu V^2/Hz$	2,64	0,077	0,437	4,52	10^{-6}
Frequency- β , Hz	1,68	0,192	0,420	4,29	10^{-6}
Fp2- α PSD, $\mu V^2/Hz$	2,05	0,136	0,401	4,15	10^{-6}
O1- δ PSD, %	2,01	0,140	0,383	4,02	10^{-6}
PSD HF, %	1,95	0,149	0,366	3,92	10^{-6}
F3- α PSD, %	1,69	0,192	0,352	3,79	10^{-6}
T5- α PSD, $\mu V^2/Hz$	2,07	0,133	0,335	3,73	10^{-6}
Index- β , %	1,46	0,238	0,323	3,61	10^{-6}
Deviation- δ , Hz	1,50	0,228	0,312	3,52	10^{-6}
T5- δ PSD, $\mu V^2/Hz$	1,38	0,258	0,301	3,42	10^{-6}
F4- δ PSD, %	1,51	0,226	0,290	3,34	10^{-6}
Heart Rate, bpm	1,19	0,309	0,281	3,25	10^{-6}
Mode HRV, msec	1,57	0,215	0,270	3,19	10^{-6}
PSD VLF, msec ²	1,07	0,348	0,263	3,10	10^{-6}
T6- δ PSD, $\mu V^2/Hz$	1,13	0,328	0,255	3,03	10^{-6}
Laterality- δ , %	1,62	0,204	0,244	2,99	10^{-6}
F8- δ PSD, $\mu V^2/Hz$	1,29	0,283	0,235	2,94	10^{-6}
P3- δ PSD, %	1,18	0,313	0,228	2,88	10^{-6}
Laterality- α , %	1,44	0,245	0,219	2,84	10^{-6}

The rest of the variables were outside the discriminant model, probably due to duplication or redundancy of identifying information (Table 3).

Table 3. Discriminant Function Analysis Summary for EEG&HRV Variables currently not in the Model

Variables	Groups (n)			Parameters of Wilk's Statistics					Reference (112)	Cv
	Control Waters (15)	Base-line (80)	Tested Water B-P+(5)	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerance		
O1- δ PSD, $\mu V^2/Hz$	102 28	107 17	39 15	0.218	0.996	0.121	0.886	0.249	98 8	0.840
F7- θ PSD, $\mu V^2/Hz$	14.2 3.1	15.0 1.7	5.0 1.9	0.217	0.993	0.260	0.772	0.213	18.2 1.4	0.843
F8- θ PSD, $\mu V^2/Hz$	11.5 1.7	12.3 0.8	6.1 2.0	0.218	0.995	0.177	0.838	0.132	20.4 2.5	1.324
T5- θ PSD, $\mu V^2/Hz$	23.5 4.1	21.8 2.4	10.0 2.8	0.216	0.987	0.447	0.641	0.201	28,7 2.5	0.906
T6- θ PSD, $\mu V^2/Hz$	19.1 3.3	17.0 1.6	7.7 2.5	0.219	0.998	0.057	0.945	0.266	23.2 1.9	0.869
Fp1- α PSD, %	48.9 5.1	38.5 2.4	30.6 6.7	0.218	0.994	0.200	0.819	0.072	35.1 1.4	0.423
Fp2- α PSD, %	43.5 4.6	35.9 2.3	21.2 3.6	0.218	0.996	0.139	0.870	0.042	32.9 1.4	0.448
T3- α PSD, %	43.2 3.8	33.2 2.0	29.8 2.5	0.218	0.994	0.222	0.802	0.077	30.4 1.4	0.483
T3- β PSD, %	31.4 4.5	33.8 1.7	47.9 7.0	0.217	0.993	0.255	0.776	0.226	30.7 1.3	0.462
RMSSD, msec	17.0 1.6	21.4 0.9	20.8 2.3	0.218	0.997	0.116	0.890	0.180	30.3 1.4	0.474
PSD LFnu, %	82.3 2.2	76.8 1.4	79.4 6.0	0.219	0.999	0.036	0.964	0.136	65.4 1.2	0.193

The identifying information contained in the 28 discriminant variables is condensed into two roots. The major root contains 69.5% of discriminatory opportunities ($r^*=0.789$; Wilks' $\Lambda=0.219$; $\chi^2_{(56)}=127$; $p<10^{-6}$), minor root 30.5% ($r^*=0.648$; Wilks' $\Lambda=0.580$; $\chi^2_{(27)}=45$; $p=0.014$).

The next goal of discriminant analysis is visualization of each participant in the information space of roots (Fig. 3). It is achieved by calculating the values of discriminant roots for each person by the raw coefficients and the constants (Table 4).

Table 4. Standardized and raw coefficients and constants for discriminant EEG variables

Variables	Coefficients	Standardized		Raw	
		Root 1	Root 2	Root 1	Root 2
Asymmetry- δ , %		0,610	0,236	0,018	0,007
C4- α PSD, %		3,207	1,225	0,170	0,065
C3- α PSD, %		-2,004	1,382	-0,106	0,073
Deviation- α , Hz		-0,422	0,439	-0,727	0,757
T5- δ PSD, %		-0,859	0,660	-0,057	0,044
Fp1- θ PSD, $\mu V^2/Hz$		-0,574	-0,793	-0,043	-0,060
Asymmetry- β , %		-0,134	-0,766	-0,008	-0,048
PSD HF, msec ²		0,350	-0,052	0,0030	-0,0004
Fp2- δ PSD, %		0,534	-0,316	0,024	-0,014
F8- α PSD, $\mu V^2/Hz$		-0,826	0,309	-0,022	0,008
Frequency- β , Hz		0,363	0,421	0,090	0,105
Fp2- α PSD, $\mu V^2/Hz$		2,115	0,633	0,018	0,005
O1- δ PSD, %		-0,093	0,195	-0,006	0,012
PSD HF, %		-0,655	-0,079	-0,124	-0,015
F3- α PSD, %		-1,704	-2,298	-0,090	-0,122
T5- α PSD, $\mu V^2/Hz$		-0,844	0,313	-0,006	0,002
Index- β , %		-0,350	0,296	-0,018	0,016
Deviation- δ , Hz		-0,355	0,048	-1,266	0,170
T5- δ PSD, $\mu V^2/Hz$		0,902	0,278	0,008	0,003
F4- δ PSD, %		0,231	-0,591	0,015	-0,039
Heart Rate, bpm		-1,269	2,120	-0,103	0,172
Mode HRV, msec		-0,921	2,011	-0,006	0,014
PSD VLF, msec ²		-0,527	-0,445	-0,0010	-0,0009
T6- δ PSD, $\mu V^2/Hz$		-0,394	-0,747	-0,004	-0,008
Laterality- δ , %		0,281	0,883	0,009	0,027
F8- δ PSD, $\mu V^2/Hz$		-0,483	-0,133	-0,0040	-0,0011
P3- δ PSD, %		-0,040	0,788	-0,003	0,059
Laterality- α , %		-0,144	-0,511	-0,006	-0,022
Constants				16,97	-28,37
Eigenvalues				1,650	0,724
Cumulative Proportions				0,695	1

Ignoring mathematical formalities, we still included in Table 5 11 variables that were not included in the discriminant model, since they organically fit into the factorial structure of the roots.

Table 5. Correlations between variables and roots; centroids of clusters, and Z-scores

Variables	Correlations Variables-Roots		Control Waters (15)	Baseline (80)	Tested Water B-P+(5)	Clu- sters (Figs. 1&2)
Root 1 (69,5%)	Root 1	Root 2	-0,43	-0,26	5,51	
Asymmetry- δ	0,303	0,028	-0,14 $\pm$ 0,35	-0,13 $\pm$ 0,15	2,21 $\pm$ 0,64	I
Fp2- δ PSDr	0,188	-0,066	-0,25 $\pm$ 0,27	-0,02 $\pm$ 0,14	1,24 $\pm$ 0,66	I
T3- β PSDr			0,05 $\pm$ 0,32	0,22 $\pm$ 0,12	1,21 $\pm$ 0,50	I
Frequency- β	0,183	0,076	0,66 $\pm$ 0,23	0,52 $\pm$ 0,10	1,52 $\pm$ 0,52	I
Laterality- δ	0,154	0,031	0,01 $\pm$ 0,17	-0,02 $\pm$ 0,09	0,71 $\pm$ 0,18	I
Laterality- α	0,063	-0,006	-0,03 $\pm$ 0,16	-0,01 $\pm$ 0,08	0,23 $\pm$ 0,10	I
Fp1- θ PSDa	-0,104	-0,110	-0,24 $\pm$ 0,12	-0,10 $\pm$ 0,07	-0,47 $\pm$ 0,12	II
T6- δ PSDa	-0,065	-0,090	-0,37 $\pm$ 0,14	-0,13 $\pm$ 0,15	-0,64 $\pm$ 0,07	II
F8- δ PSDa	-0,060	-0,085	-0,32 $\pm$ 0,12	-0,17 $\pm$ 0,09	-0,48 $\pm$ 0,07	II
P3- δ PSDr	-0,090	-0,117	-0,34 $\pm$ 0,19	-0,14 $\pm$ 0,09	-0,58 $\pm$ 0,13	II
PSD HFr	-0,100	-0,146	-0,53 $\pm$ 0,14	-0,30 $\pm$ 0,08	-0,70 $\pm$ 0,11	II
Deviation- α	-0,092	0,080	0,15 $\pm$ 0,33	-0,07 $\pm$ 0,12	-0,60 $\pm$ 0,23	III
F8- α PSDa	-0,085	0,110	0,14 $\pm$ 0,18	-0,07 $\pm$ 0,09	-0,39 $\pm$ 0,12	III
T5- α PSDa	-0,087	0,093	0,11 $\pm$ 0,30	-0,10 $\pm$ 0,10	-0,51 $\pm$ 0,09	III
T5- δ PSDa	-0,087	0,128	0,07 $\pm$ 0,40	-0,21 $\pm$ 0,08	-0,59 $\pm$ 0,05	III
Deviation- δ	-0,127	0,111	0,37 $\pm$ 0,31	0,07 $\pm$ 0,12	-0,64 $\pm$ 0,00	III
Index- β	-0,094	0,155	-0,14 $\pm$ 0,16	-0,78 $\pm$ 0,20	-1,54 $\pm$ 0,47	IV
O1- δ PSDa			0,05 $\pm$ 0,34	0,11 $\pm$ 0,21	-0,71 $\pm$ 0,19	V
T5- δ PSDr	-0,129	0,010	-0,20 $\pm$ 0,21	-0,23 $\pm$ 0,09	-0,84 $\pm$ 0,22	V
F8- θ PSDa			-0,33 $\pm$ 0,06	-0,30 $\pm$ 0,03	-0,53 $\pm$ 0,07	V
T5- θ PSDa			-0,20 $\pm$ 0,16	-0,27 $\pm$ 0,09	-0,72 $\pm$ 0,11	V
T6- θ PSDa			-0,20 $\pm$ 0,16	-0,31 $\pm$ 0,08	-0,77 $\pm$ 0,12	V
F7- θ PSDa			-0,26 $\pm$ 0,21	-0,21 $\pm$ 0,11	-0,86 $\pm$ 0,13	V
Root 2 (30,5%)	Root 1	Root 2	1,97	-0,38	0,17	
Heart Rate	-0,076	0,273	1,84 $\pm$ 0,37	0,87 $\pm$ 0,16	0,40 $\pm$ 0,46	VI
I/Mode HRV	-0,046	0,236	1,57 $\pm$ 0,25	0,78 $\pm$ 0,16	0,56 $\pm$ 0,48	VI
F3- α PSDr	-0,042	0,255	0,98 $\pm$ 0,23	0,26 $\pm$ 0,14	0,14 $\pm$ 0,35	VI
C3- α PSDr	-0,043	0,261	0,81 $\pm$ 0,24	0,10 $\pm$ 0,13	-0,02 $\pm$ 0,39	VI

T3- α PSDr			0,87 $\pm$ 0,26	0,19 $\pm$ 0,13	-0,04 $\pm$ 0,17	VI
Fp2- α PSDa	-0,075	0,122	0,84 $\pm$ 0,44	0,36 $\pm$ 0,18	-0,22 $\pm$ 0,33	VII
Fp1- α PSDr			0,93 $\pm$ 0,34	0,23 $\pm$ 0,16	-0,31 $\pm$ 0,45	VII
Fp2- α PSDr			0,72 $\pm$ 0,31	0,21 $\pm$ 0,16	-0,79 $\pm$ 0,25	VII
PSD LFau			1,47 $\pm$ 0,23	1,05 $\pm$ 0,13	1,26 $\pm$ 0,60	VIII
C4- α PSDr	0,024	0,229	0,77 $\pm$ 0,27	0,09 $\pm$ 0,15	0,43 $\pm$ 0,46	VIII
Asymmetry- β	0,007	-0,270	-0,62 $\pm$ 0,12	0,02 $\pm$ 0,12	-0,09 $\pm$ 0,47	IX
F4- δ PSDr	0,005	-0,199	-0,65 $\pm$ 0,10	-0,29 $\pm$ 0,09	-0,35 $\pm$ 0,26	IX
RMSSD			-0,93 $\pm$ 0,16	-0,45 $\pm$ 0,10	-0,30 $\pm$ 0,38	IX
O1- δ PSDr	-0,051	-0,142	-0,65 $\pm$ 0,12	-0,32 $\pm$ 0,13	-0,70 $\pm$ 0,23	X
PSD VLFa	-0,070	-0,193	-1,13 $\pm$ 0,11	-0,75 $\pm$ 0,10	-1,01 $\pm$ 0,27	X
PSD HFa	-0,098	-0,236	-1,05 $\pm$ 0,05	-0,69 $\pm$ 0,09	-0,99 $\pm$ 0,24	X

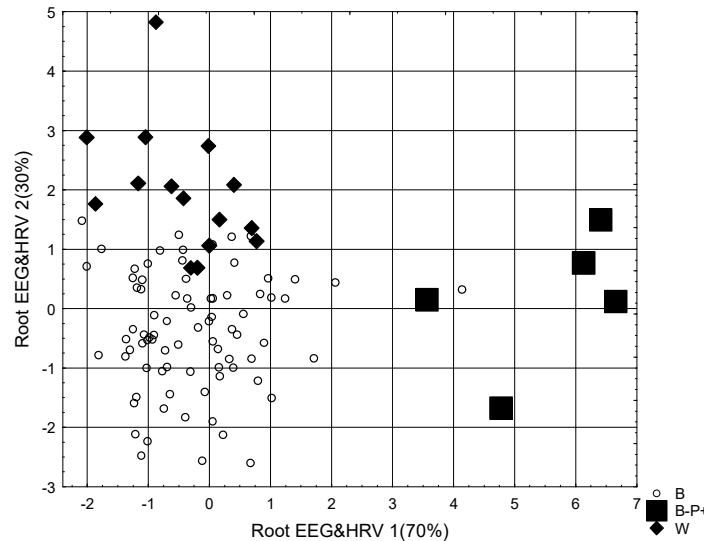


Fig. 3. Scattering of individual values of discriminant roots **before** (B) and 1.5 h after consumption of 30 ml of **control waters** (well, distilled, tap water filtered) (W) and 30 ml of distilled water with false notification to the recipients that water was **processed** by the Babelyuk (B-P+)

The displacement of localization along the axis of the major root of the cluster of Tested Water relative to the basal cluster reflects both the enhancing of the variables associated with the root positively and the inhibition of the variables associated with it negatively. At the same time, the projections on the axis of individual roots after the use of CWs are mixed with the projections of the basal cluster, which reflects the absence of changes in these same variables.

Instead, the CWs cluster is shifted relative to the basal cluster along the minor root axis, which reflects the enhancing/inhibition of another constellation of variables whose information is condensed in this root, while Tested Water does not significantly affect these variables.

Fig. 4 illustrates the sufficient stability of both the basal EEG&HRV parameters and 1.5 hours after the use of CWs, in the participants of the experiment during the period from October 10 to November 19 2010. This is important for the announced comparative assessment of the neurotropic effects of other factors.

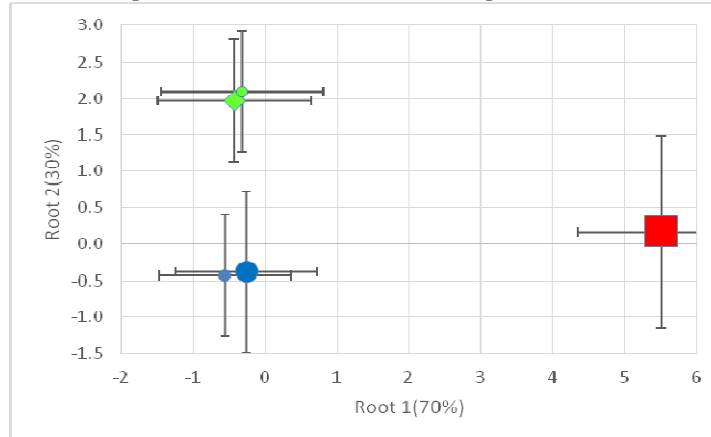


Fig. 4. Average (Mean $\pm$ SD) values of discriminant roots **before** and 1.5 h after consumption of 30 ml of **control waters** (well, distilled, tap water filtered) and 30 ml of distilled water with false notification to the recipients that water was **processed** by the Babelyuk.

Small markers refer only to this experiment ($n=17$ and 12 for baseline and control waters respectively), large markers refer to the entire series ($n=80$ and 15 respectively)

Despite some mixing, the demarcation of three clusters in the information space of two roots is highly reliable (Table 6).

Table 6. Squares of Mahalanobis distances between groups (above the diagonal) and F-criteria ($df=28,7$) as well as p-levels (below the diagonal)

Groups	Baseline (80)	Tested Water B-P+(5)	Control Waters (15)
Baseline	0	33,6	5,6
Tested Water	4,08 10^{-6}	0	38,5
Control Waters	1,82 0,023	3,72 10^{-5}	0

Another consequence of discriminant analysis is the possibility to retrospectively identify one or another state of each participant: basal and after drinking control or tested water. This goal of discriminant analysis is realized with the help of coefficients and constants of classification functions (Table 7).

Table 7. Coefficients and constants of classification functions

Groups	Baseline (80)	Tested Water B-P+(5)	Control Waters (15)
Variables	$p=0,80$	$p=0,05$	$p=0,15$
Asymmetry- δ , %	0,172	0,281	0,186
C4- α PSD, %	1,812	2,830	1,937
C3- α PSD, %	2,200	1,631	2,389
Deviation- α , Hz	21,38	17,60	23,28
T5- δ PSD, %	1,794	1,489	1,907
Fp1- θ PSD, $\mu V^2/Hz$	2,649	2,367	2,516
Asymmetry- β , %	-0,604	-0,679	-0,715
PSD HF, msec ²	-0,383	-0,366	-0,385
Fp2- δ PSD, %	0,246	0,379	0,208
F8- α PSD, $\mu V^2/Hz$	0,910	0,788	0,933
Frequency- β , Hz	6,032	6,611	6,263
Fp2- α PSD, $\mu V^2/Hz$	-0,681	-0,573	-0,671
O1- δ PSD, %	-1,247	-1,274	-1,217
PSD HF, %	3,712	2,991	3,697
F3- α PSD, %	-0,864	-1,452	-1,136
T5- α PSD, $\mu V^2/Hz$	0,272	0,239	0,278
Index- β , %	0,476	0,378	0,516
Deviation- δ , Hz	44,75	37,54	45,37
T5- δ PSD, $\mu V^2/Hz$	-0,643	-0,595	-0,639
F4- δ PSD, %	0,556	0,622	0,461
Heart Rate, bpm	46,50	46,00	46,92
Mode HRV, msec	4,029	3,999	4,063
PSD VLF, msec ²	0,026	0,020	0,024
T6- δ PSD, $\mu V^2/Hz$	-0,042	-0,070	-0,060
Laterality- δ , %	-0,031	0,034	0,032
F8- δ PSD, $\mu V^2/Hz$	0,107	0,083	0,105
P3- δ PSD, %	3,375	3,390	3,514
Laterality- α , %	0,203	0,155	0,152
Constants	-3589	-3524	-3662

It is significant that the condition of the participants after using Test water is recognized without error, despite their small number. The low classification accuracy of the control group reflects, apparently, a generally weak effect on the EEG&HRV parameters of CWs (Table 8).

Table 8. Classification Matrix

Group	Rows: Observed classifications Columns: Predicted classifications			
	Percent Correct	B $p=,80000$	B-P+ $p=,05000$	CW $p=,15000$
Baseline	97,5	78	1	1
B-P+	100,0	0	5	0
CW	60,0	6	0	9
Total	92,0	84	6	10

Discussion

The information presented in Figs. 1 and 2, was later reformatted in such a way as to put Placebo effects and their ranking in the foreground (Figs. 5 and 6). However, we consider it necessary to start a discussion on the effects of Control Waters.

It is known that the inner preconditions are changed systematically by the spontaneous long wave rhythms synchronous to the earthly environment, i.e. to the circadian rhythms (Hildebrandt, 1980). It seems unlikely to us that the detected significant changes in EEG&HRV parameters 1.5 hours after drinking only 30 ml of ordinary waters at room temperature are caused by water itself (*postquam non significat propter hoc* - after that does not mean consequently, in Latin). Their interpretation as **spontaneous rhythmic changes** (the term is borrowed by us from Hildebrandt, 1980) is much more likely.

Regarding HRV parameters, we found (Fig. 5) a significant decrease in RMSSD (as a marker of vagal tone) and an increase in LFnu (as a marker of sympathetic tone) as well as 1/Mode and heart rate (as markers of circulating catecholamines and other positive chronotropic factors). This is consistent with the data of other authors about the opposite changes in HRV parameters in the period between 6 and 13 hours of daily monitoring (Nakagawa et al., 1998; Vandewalle et al., 2007; Sztajzel et al., 2008; Li et al., 2011; Rodríguez-Colón et al., 2014; Black et al., 2019; Deng et al., 2022), because in our experiment HRV&EEG registration was carried out at 9-9.30 and 10.30-11. In addition, we found a significant increase in the PSD of α -rhythm generating neurons that project to Fp1, Fp2, F3, T3, C3, and C4 loci as well as δ -rhythm generating neurons that project to the T5 locus, instead of a decrease in PSD in F4 locus against the background of increased δ -rhythm variability and β -rhythm index.

We were not lucky to find information on spontaneous rhythmic changes in EEG parameters at human on PubMed and PMC resources. It is interesting that in the review "Circadian Rhythms and Measures of CNS/Autonomic Interaction" (Riganello et al., 2019) after the sentence "There is full evidence of a complex interaction between the central and autonomic nervous systems, with a two-way modulation of, and by, circadian rhythms", no source is given regarding EEG or fMRI parameters. Therefore, there are probably no such sources.

Only recently Masuda et al. (2023) examined at **mice** changes in circadian sleep-wake behavior using circadian components extracted from EEG and EMG data. EEG and EMG were recorded from mice for 3 days under light/dark and constant dark conditions. Authors analyzed time-dependent changes in the duration of sleep. REM and NREM sleep significantly increased during the night phase, whereas no significant change was observed during the light phase. Authors concluded that EEG/EMG analysis is useful not only for evaluating sleep-wake stages but also for *circadian rhythms in the brain*.

It is obvious that the essential (*per se*) **Placebo Effects** should be evaluated by the algebraic difference between the **effects of Tested Water** and spontaneous rhythmic changes. Applying this approach, we state that in the absence of effects of **Tested Water** on both RMSSD, Asymmetry of β -rhythm, PSD F4- δ r, and C3- α , F3- α , T3- α , 1/Mode, essential **Placebo Effects de facto** are enhancing and inhibitory respectively (Fig. 5).

It is appropriate to distinguish 4 qualitative-quantitative clusters of **Placebo Effects**: **enhancing (n=9)**, **weak inhibitory (n=8)**, **moderate inhibitory (n=10)**, and **noticeably inhibitory (n=9)** (Figs. 5 and 6).

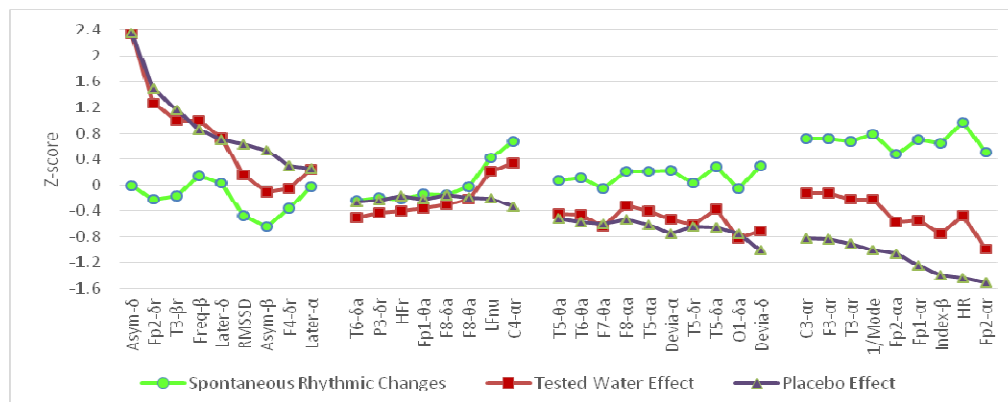


Fig. 5. Enhancing and inhibitory profiles of neurotropic Placebo Effects and accompanied effects of Tested Water (TW) as well as spontaneous rhythmic changes (SRCh).

Spontaneous rhythmic changes calculated by equation: **SRCh** = **CWs** - **Baseline**; **TW Effect** = **TW** - **Baseline**; **Placebo Effects** = **TW Effects** - **SRCh**

The most noticeable **Placebo Effect** was the induction of asymmetry of the δ -rhythm, or rather its rightward shift, due to an increase in PSD in the right loci (Fp2 and F4). The effect on the asymmetry of the β -rhythm (due to the T3 locus) and the minimal effect on the asymmetry of the α -rhythm (due to the reduction of PSD in the left Fp1, F3, T3, C3 and T5 loci) turned out to be less pronounced.

Despite this, the asymmetry of just the α -rhythm in frontal loci (FAA) is considered as a neurobiological correlate of the positive effect of placebo on the performance (**ergogenic** placebo effect, EPE). Administering a placebo ergogenic aid significantly influenced FAA during maximum effort cycling (Broelz et al., 2019). The main findings of this study indicate, that athletes who received a placebo ergogenic aid showed an increase in FAA during a cycling time trial compared to athletes who received no intervention.

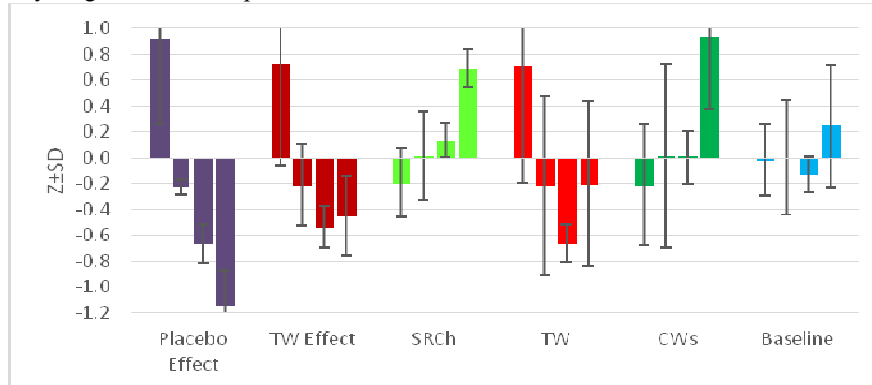


Fig. 6. Enhancing (first column, n=9), weak inhibitory (second column, n=8), moderate inhibitory (third column, n=10), and noticeably inhibitory (fourth column, n=9) clusters of neurotropic Placebo Effects and accompanied effects of **Tested Water** (TW) as well as spontaneous rhythmic changes (**SRCh**). Spontaneous rhythmic changes calculated by equation: **SRCh** = **CWs** – **Baseline**; **TW Effect** = **TW** – **Baseline**; **Placebo Effects** = **TW Effects** - **SRCh**

The induction of asymmetry is accompanied by an increase in vagal tone, but it is correlated only with laterality of δ -rhythm ($r=0.25$) as well as deviation of α -rhythm ($r=-0.36$) (Table 9).

Table 9. Correlation Matrix for EEG and HRV variables

Variables	RMSSR	VLFa	HFa	HF _r	LFnu	HR	1/Mode
RMSSD, msec	1	0,51	0,82	0,27	-0,17	-0,35	-0,39
PSD VLF, msec ²	0,51	1	0,65	-0,15	-0,09	-0,32	-0,36
PSD HF, msec ²	0,82	0,65	1	0,37	-0,24	-0,24	-0,29
PSD HF, %	0,27	-0,15	0,37	1	-0,75	-0,34	-0,33
PSD LFnu, %	-0,17	-0,09	-0,24	-0,75	1	0,63	0,60
Heart Rate, bpm	-0,35	-0,32	-0,24	-0,34	0,63	1	0,98
1/Mode HRV, msec	-0,39	-0,36	-0,29	-0,33	0,60	0,98	1
Deviation- α , Hz	-0,36	-0,19	-0,28	0,19	-0,30	-0,25	-0,22
Laterality- α , %	0,05	-0,27	-0,03	0,26	-0,16	-0,03	0,00
Fp1- α PSD, %	0,03	0,07	0,09	-0,24	0,38	0,52	0,51
Fp2- α PSD, %	0,01	0,04	0,10	-0,16	0,38	0,49	0,48
Fp2- α PSD, $\mu V^2/Hz$	0,03	0,09	0,10	-0,19	0,33	0,50	0,49
F3- α PSD, %	-0,03	-0,04	0,02	-0,22	0,40	0,56	0,57
F8- α PSD, $\mu V^2/Hz$	0,03	0,15	0,08	-0,19	0,22	0,33	0,34
T3- α PSD, %	0,03	0,10	0,10	-0,20	0,31	0,46	0,47
C3- α PSD, %	-0,00	0,01	0,06	-0,22	0,40	0,56	0,56
C4- α PSD, %	0,01	0,06	0,09	-0,18	0,34	0,49	0,50
Fp1- θ PSD, $\mu V^2/Hz$	-0,00	0,03	0,09	-0,05	0,16	0,31	0,34
T5- θ PSD, $\mu V^2/Hz$	-0,10	0,10	0,00	-0,18	0,22	0,29	0,30
T6- θ PSD, $\mu V^2/Hz$	0,02	0,13	0,11	-0,12	0,15	0,32	0,30
T5- α PSD, $\mu V^2/Hz$	0,01	0,20	0,09	-0,22	0,24	0,36	0,37
Asymmetry- β , %	-0,12	-0,10	-0,11	0,03	0,04	0,23	0,23
Frequency- β , Hz	-0,13	-0,28	-0,22	0,06	0,14	0,10	0,15
T3- β PSD, %	-0,01	-0,08	-0,08	0,10	-0,07	-0,23	-0,24
Asymmetry- δ , %	-0,11	-0,12	-0,14	0,08	-0,26	-0,15	-0,12
Laterality- δ , %	0,25	-0,03	0,12	0,11	-0,09	-0,09	-0,09
Fp2- δ PSD, %	0,04	0,10	0,02	-0,03	-0,24	-0,19	-0,17
F4- δ PSD, %	0,14	0,19	0,13	0,03	-0,21	-0,29	-0,29
F8- δ PSD, $\mu V^2/Hz$	0,19	0,39	0,31	-0,05	-0,05	-0,10	-0,13
P3- δ PSD, %	-0,04	0,08	0,01	0,06	-0,23	-0,20	-0,22
O1- δ PSD, $\mu V^2/Hz$	-0,10	0,10	0,00	-0,21	0,19	0,24	0,21

Note. According to the equation: $|r| = \{\exp[2t/(n-1.5)^{0.5}] - 1\} / \{\exp[2t/(n-1.5)^{0.5}] + 1\}$ for a sample of $n=100$ critical value $|r|$ at $p<0.05$ ($t>1.98$) is 0.20, $p<0.01$ ($t>2.62$) is 0.26, $p<0.001$ ($t>3.37$) is 0.33

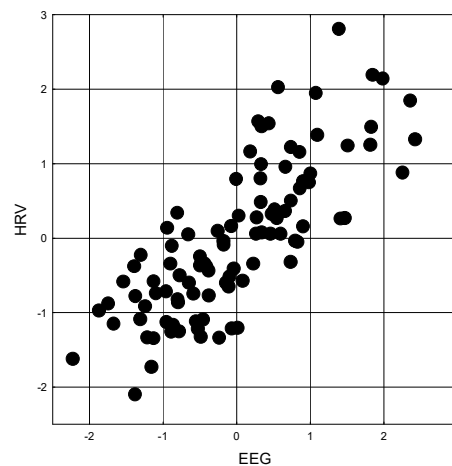
A larger number of EEG parameters are subject to the inhibitory effect of placebo, which is accompanied by a decrease in sympathetic tone and the level of circulating catecholamines and heart rate. The sympathoinhibitory effect of placebo is associated with inhibition of the activity of α -rhythm generating neurons in many loci and activation of δ -rhythm generating neurons in Fp2, F4, P3 and O1 loci as well as induction of

asymmetry of δ -rhythm ($r=-0.26$) and deviation of α -rhythm ($r=-0.30$). A decrease in the level of circulating catecholamines and HR is associated with the same neurotropic effects of placebo, as well as inhibition of the activity of θ -rhythm generating neurons in Fp1, T5 and T6 loci as well as asymmetry of β -rhythm ($r=0.23$) (Table 9).

As a result of the canonical correlation analysis of the relationships between EEG and HRV parameters, two pairs of roots were found. HRV-root of the first pair represents primarily sympatho-adrenal markers, which are upregulated by α - and θ -rhythm generating neurons while downregulated by δ - and β -rhythm generating (Table 10).

Table. 10. Factor structure of first pair of EEG and HRV canonical Roots

EEG variables	Root 1
C3- α PSD, %	-0,724
F3- α PSD, %	-0,723
Fp2- α PSD, %	-0,685
Fp2- α PSD, $\mu V^2/Hz$	-0,649
Fp1- α PSD, %	-0,678
C4- α PSD, %	-0,650
T3- α PSD, %	-0,598
T5- α PSD, $\mu V^2/Hz$	-0,471
F8- α PSD, $\mu V^2/Hz$	-0,431
Deviation- α , Hz	0,460
Fp1- θ PSD, $\mu V^2/Hz$	-0,377
T6- θ PSD, $\mu V^2/Hz$	-0,377
T5- θ PSD, $\mu V^2/Hz$	-0,371
O1- δ PSD, $\mu V^2/Hz$	-0,281
Asymmetry- β , %	-0,235
T3- β PSD, %	0,213
Fp2- δ PSD, %	0,378
F4- δ PSD, %	0,368
P3- δ PSD, %	0,335
Asymmetry- δ , %	0,369
Laterality- δ , %	0,095
HRV variables	Root 1
Heart Rate, bpm	-0,898
1/Mode HRV, msec	-0,854
PSD LFnu, %	-0,795
PSD HF, %	0,368



$R=0.787$; $R^2=0.620$; $\chi^2_{(168)}=271$; $p=10^{-6}$; $\Lambda_{\text{Prime}}=0.038$

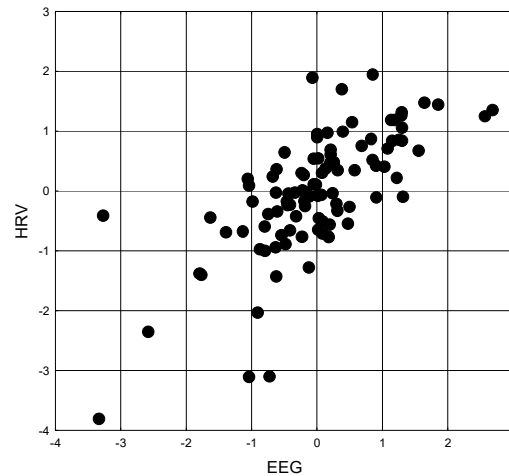
Fig. 6. Scatterplot of canonical correlation between EEG (X-line) and HRV (Y-line) parameters. First pair of Roots

A separate marker of vagal tone (PSD HF relative), upregulated by deviation of α -rhythm. The rate of EEG/HRV determination is 62% (Fig. 6).

The HRV-root of the second pair is primarily represented by vagal markers and, to a lesser extent, sympatho-adrenal markers, which are subject to opposite influences from δ -rhythm generating neurons. Another regulatory factor is the asymmetry and variability of β - and α -rhythms (Table 11). The rate of EEG/HRV determination in this pair is much weaker - 49% (Fig. 7).

Table. 11. Factor structure of second pair of EEG and HRV canonical Roots

EEG variables	Root 2
F8- δ PSD, $\mu V^2/Hz$	-0,556
F4- δ PSD, %	-0,272
O1- δ PSD, $\mu V^2/Hz$	-0,201
Fp2- δ PSD, %	-0,196
Frequency- β , Hz	0,506
Deviation- α , Hz	0,450
Laterality- α , %	0,347
Asymmetry- β , %	0,146
HRV variables	Root 2
PSD VLF, msec ²	-0,926
PSD HF, msec ²	-0,725
RMSSD, msec	-0,619
1/Mode HRV, msec	0,229
Heart Rate, bpm	0,171



$R=0.702$; $R^2=0.492$; $\chi^2_{(138)}=191$; $p=0.002$; $\Lambda \text{ Prime}=0.100$

Fig. 7. Scatterplot of canonical correlation between EEG (X-line) and HRV (Y-line) parameters. Second pair of Roots

Our data fit into the framework of the concept of a central autonomic network (Benarroch, 1993; Palma & Benarroch, 2014) and, in principle, are consistent with the data of other authors (Van Buren & Ajmone-Marsan, 1960; Thayer & Lane, 2009; Sakaki et al., 2016; Winkelmann et al., 2017; Yoo et al., 2018; Carnevali et al., 2020; Matusik et al., 2023; Borghesi et al., 2024) as well as our previous studies with other participants (Popovych et al., 2014; Popadynets et al., 2020; Gozhenko et al., 2021; Popovych, 2022; Popovych et al., 2022; Zukow et al., 2022; Popovych et al., 2024). An emerging literature is demonstrating that cognitive and emotional processes that are engaged during the administration of an otherwise inactive agent, a placebo, are capable of activating internal mechanisms that modify physiology.

A network of regions, including the rostral anterior cingulate, dorsolateral prefrontal and orbitofrontal cortices, insula, nucleus accumbens, amygdala, medial thalamus and periaqueductal gray appear involved. Opioid and dopamine neurotransmission in these areas modulate various elements of the placebo effect, which appear to include the representation of its subjective value, updates of expectations over time, changes in affective state and in pain ratings (review: Zubieta et al., 2009).

It is known that in both experimental and clinical scenarios, the placebo response varies tremendously among individuals. The individual placebo response can range from no effect (non-responders) to profound changes in symptoms or disease severity (responders) (Enck et al., 2013).

All participants of our study were responders, but their reactions to placebo were different in terms of expressiveness and trajectory. In particular, in the participant Sh **expressiveness** of placebo response variables, the information about which is condensed in the **first** Root, is much **smaller** than that of others. In the participant Ly, the **direction** of placebo response variables, the information about which is condensed in the **second** Root, is **opposite** to that of the others (Fig. 8).

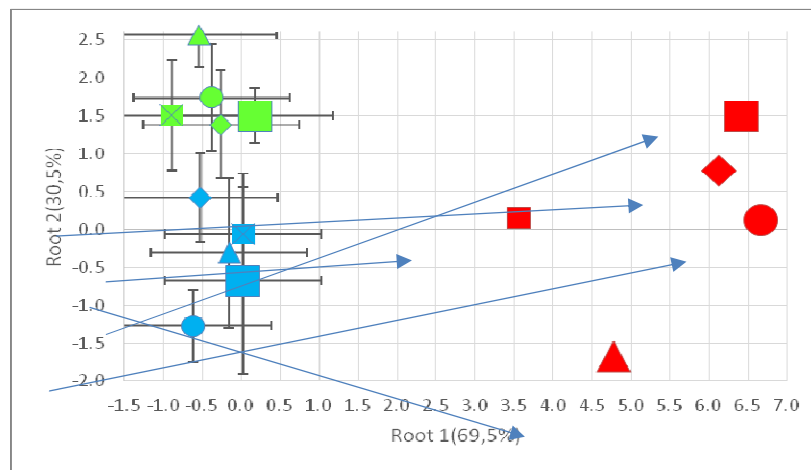


Fig. 8. Scattering of individual values of discriminant roots **before** and **1.5 h after** consumption of 30 ml of distilled water with false notification to the recipients that water was **processed** by the Babelyuk, as well as **control waters**. The mean baseline ($M \pm SD$, $n=6 \div 13$) of each recipient is shown (Po circle, Ba rhombus, Ly triangle, Le square, Sh square with diagonals)

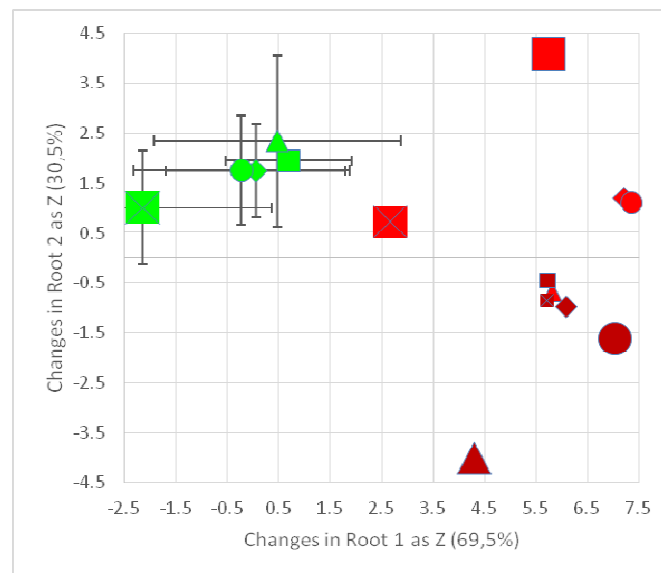


Fig. 9. Scattering of individual changes in discriminant roots 1.5 h after consumption of 30 ml of distilled water with false notification to the recipients that water was **processed** by the Babelyuk, and **Control waters** ($Mean \pm SD$, $n=3$). Individual essential **Placebo effects** calculated as differences between changes in discriminant roots 1.5 h after consumption of **Tested water** and **Control waters**. The markers of the recipients: Po circle, Ba rhombus, Ly triangle, Le square, Sh square with diagonals

Essential placebo effects, calculated taking into account spontaneous rhythmic changes (Fig. 9), in the three participants turned out to be almost the same in relation to the variables associated with both major and minor roots. These participants had similar levels of trait anxiety (Le 39, Sh 40, Ba 46).

Participant Ly (trait anxiety 51) had weaker essential placebo effects for major root variables, but stronger ones for minor root variables. Finally, in participant Po (trait anxiety 59), essential placebo effects turned out to be maximal in relation to all variables.

We revealed a relationship of medium strength between individual levels of Root 1 (in which information about 17 variables is condensed) before and 1.5 h after consumption of **Tested water** (Fig. 10, right) as well as Root 1 of **Placebo effect** (Fig. 10, left).

It is interesting that the markers of participants Le and Sh along the Y axis diverge maximally in the first case, but almost coincide in the second case, while the trajectories of the other participants are almost the same in both cases.

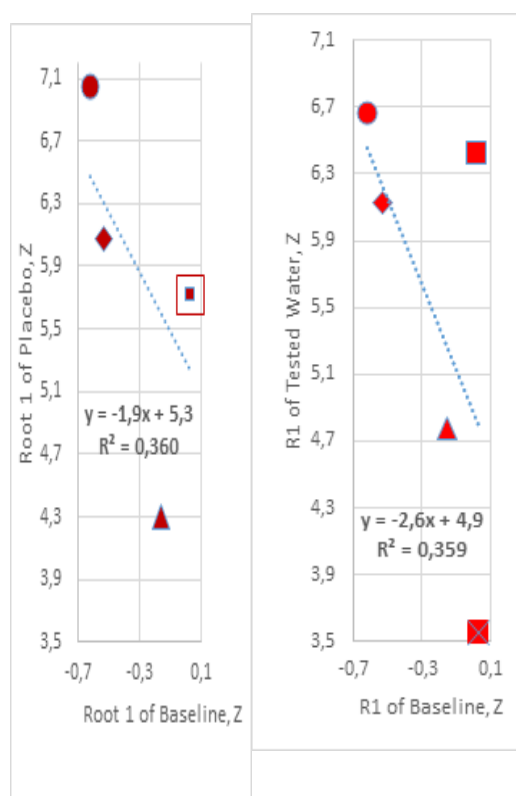


Fig. 10. Relationships between individual levels of discriminant Roots 1 before (X-line) and 1.5 h after consumption of 30 ml of **Tested water** (Y-line, right) as well as Roots 1 of **Placebo effect** (Y-line, left) calculated by subtracting of spontaneous rhythmic changes. *The markers of the recipients: Po circle, Ba rhombus, Ly triangle, Le square with diagonals*

Enck et al. (2013; 2018) emphasize that in order to systematically utilize placebo responses, it is essential to predict the capacity of an individual to develop placebo responses in a context-, physiological system- and disease-specific manner. Thus, identifying predictor variables for placebo responders or non-responders would be of great value for the effective use of placebo responses in the optimization of treatment outcomes in clinical practice, as well as for the design and interpretation of clinical trials. Much effort is currently being dedicated to the identification of psychological, neuroendocrine or genetic variables that moderate an individual's placebo responsiveness in different physiological systems and diseases. There is evidence supporting the putative relevance of several psychosocial variables in mediating placebo responses. These variables include: **trait and state anxiety; patients' expectations** (*highlighted by us as a spoiler*), dispositional optimism and hypnotic suggestibility; health locus of control; cultural variations in anxiety disorders; and coping abilities. Evidence supporting the role of genetic traits in moderating placebo responses is best documented in anxiety disorders and depression. The latest evidence from diffusion tensor imaging in healthy volunteers supports the notion that individual brain anatomy also predicts an individual's capacity to develop placebo analgesia.

Certain personality traits are thought to interact with environmental cues and thereby influence neurobiological responses to treatments, indicating their role in the modulation of the placebo response. In the past, extraversion has been linked to placebo responding in irritable bowel syndrome patients, trait optimism and anxiety were shown to predict placebo and nocebo effects in analgesia and dopaminergic function associated traits like novelty seeking, harm avoidance, behavioral drive, fun seeking and reward responsiveness have been linked with placebo analgesia. A recent study showed, that a composite of three positive (ego-resiliency, altruism, straight-forwardness) and one negative (angry hostility) personality trait predicted 25% of placebo analgesia responding (review: Broelz et al., 2019). Those athletes with a more pronounced goal seeking persistence and an overall dominance of the behavioral activation system over the behavioral inhibition system (BIS) showed a significantly greater increase in FAA in response to a placebo ergogenic aid. A more pronounced BIS, however, seems to antagonize the increase in FAA associated with the ergogenic placebo response (Broelz et al., 2019).

A detailed analysis of predictors will be carried out in the next article, and now we will limit ourselves to ascertaining the role of at least *maximal expectations at Po as PhD* as well as vagal tone and trait anxiety.

It was found that the initial level of vagal tone positively determines the Placebo effect on 17 variables, condensed in the first discriminant root, by 56-74% (Fig. 11). Instead, the Placebo effect on 11 variables condensed in the second discriminant root is negatively determined by trait anxiety by 28-58% (Fig. 12).

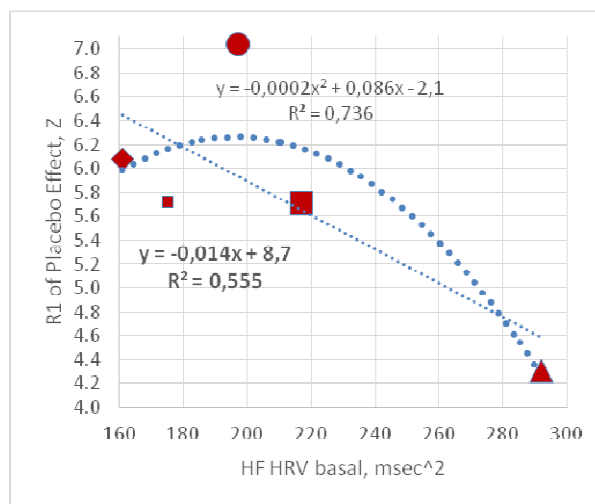


Fig. 11. Relationships between individual levels of Vagal tone (X-line) and Roots 1 of Placebo effect (Y-line)

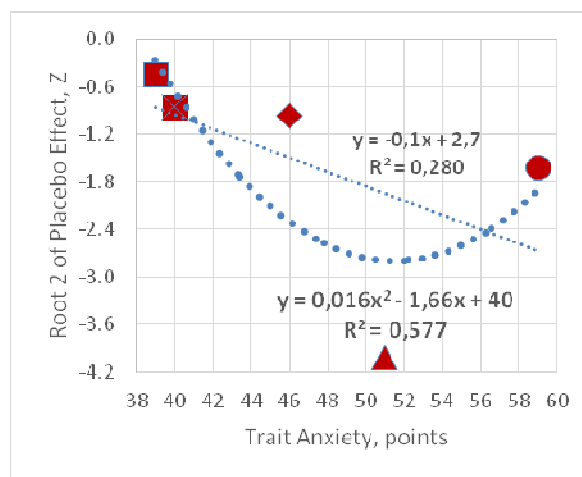


Fig. 12. Relationships between individual levels of Trait Anxiety (X-line) and Roots 2 of Placebo effect (Y-line)

Conclusions

The **ergogenic** placebo effect (EPE) has been shown in cycling using caffeine and carbohydrates, and in running using sodium bicarbonate and a hypothetical new ergogenic aid. In strength training, the EPE has been shown using anabolic steroids, amino acids and caffeine in different compound and isolation movements such as bench press, leg extension and deadlift. A review of 12 studies found overall changes in performance ranging from -7.8% to +50.7% after ergogenic placebo interventions. A meta-analysis of 14 studies reported small to moderate effects of placebo treatments in sports performance. According to a recent survey based study of 79 elite athletes from different sports, 47% of elite athletes have experienced placebo effects first hand, the majority believe in the possible ergogenic effect of placebos (82%) and those with past placebo experiences were more likely to endorse a wider use of placebos in the sport setting than those without past placebo experiences (review: Broelz et al., 2019).

Therefore, studies of the placebo effect in the field of both sports medicine and physical rehabilitation and occupational therapy are very relevant.

Limitations of this study include a relatively small sample size (5 men), which limits the generalizability of the findings. However, it should be noted that 5 participants had 100 registrations. Future studies with larger and more diverse samples will be crucial to confirm and extend these findings. In addition, while this study focused on short-term effects, it will be important to examine the long-term consequences and reproducibility of the observed changes. This study paves the way for further analyses of the neurotropic effects of other informational agents, such as Kyokushin karate kata, Sense and Cross fields, Christian prayer, and Holy water. Such studies may shed light on the neural mechanisms underlying various cultural and spiritual practices. Spoiler: this article does not include data on quasi-synchronously registered Gas Discharge Visualization parameters, which are closely related to EEG, HRV as well as Endocrine and Immune parameters (Babelyuk et al., 2017; Babelyuk et al., 2023), i.e. the elements of neuro-endocrine-immune network (Besedovsky & Sorkin, 1977; Besedovsky & del Rey, 1996).

This study makes an important contribution to our understanding of the neurophysiological basis of placebo effects. It demonstrates that even simple placebo interventions can induce complex and measurable changes in the functioning of the nervous system. As the field of placebo effects continues to evolve, studies such as this will be critical to unlocking the full potential of using placebo mechanisms to improve health care and well-being. This research aligns with the concept of placebo effects and the modulation of neurotropic responses. The study highlights the significance of psychological factors in influencing physiological outcomes, showcasing how the mind can impact the body's responses. Understanding the placebo effect is crucial in various fields, including medicine, psychology, and neuroscience, as it sheds light on the complex interactions between beliefs, expectations, and physiological processes.

The following can be said about the verification of hypotheses.

1. Hypothesis. The placebo intervention will produce measurable neurotropic effects compared to baseline and control waters. Result. Confirmed. The discriminant function analysis showed significant differences between the placebo condition (Tested Water) and both baseline and control waters ($p < 10^{-6}$). This is evidenced by the distinct clustering of the placebo condition in the discriminant roots space.

2. Hypothesis. These placebo effects will be distinguishable from spontaneous rhythmic changes that occur over time. Result. Confirmed. The study identified 17 variables that changed significantly due to spontaneous rhythmic changes. After accounting for these, additional changes were attributed to the placebo effect, demonstrating that placebo effects were distinct from spontaneous changes.

3. Hypothesis. The placebo intervention will modulate specific EEG and HRV parameters, particularly those related to autonomic nervous system activity. Result. Confirmed. The study found significant changes in various EEG parameters (e.g., asymmetry, PSD in different frequency bands) and HRV measures (e.g., Heart Rate, Mode HRV, PSD VLF, PSD HF) in response to the placebo intervention.

4. Hypothesis. The magnitude and direction of placebo effects will correlate with individual differences in baseline physiology and personality traits. Result. Partially confirmed. While the study mentioned correlations between physiological changes and personality traits (e.g., vagal tone and trait anxiety), detailed results were not provided in this particular article.

5. Hypothesis. The neurotropic effects of the placebo will involve both enhancement and inhibition of different neurophysiological parameters. Result. Confirmed. The study found an enhancing neurotropic placebo effect ($Z \pm SD$) on 9 variables (0.92 ± 0.66), a weak inhibitory effect on 8 variables (-0.23 ± 0.06), a moderate inhibitory effect on 10 variables (-0.67 ± 0.15), and a noticeable inhibitory effect on 9 variables (-1.14 ± 0.27).

6. Hypothesis. The placebo effects will be detectable using discriminant analysis of the EEG and HRV data. Result. Confirmed. The discriminant function analysis successfully distinguished between baseline, control waters, and tested water conditions with high statistical significance (Wilks' $\Lambda = 0.219$; $\chi^2(56) = 127$; $p < 10^{-6}$).

7. Hypothesis. There will be identifiable patterns or clusters of neurophysiological changes associated with the placebo intervention. Result. Confirmed. The study identified several clusters of variables that changed in response to the placebo intervention.

In terms of rejecting the null hypothesis and accepting the alternative hypothesis. The null hypothesis (H_0) that there is no difference between the placebo condition and baseline/control conditions was rejected in favor of the alternative hypothesis (H_1) that there is a significant difference. This is evidenced by the highly significant p-values ($p < 10^{-6}$) in the discriminant function analysis and the clear separation of groups in the discriminant roots space. For individual variables, the null hypothesis was rejected when the changes in response to the placebo intervention were statistically significant. This was the case for numerous EEG and HRV parameters, as detailed in Tables 1 and 2. The study provides strong evidence for the overall effect of the placebo intervention, the detailed results for some hypotheses (particularly those related to individual differences and personality traits) were not fully reported in this article, suggesting that further analysis or future studies may be needed to fully address all aspects of the initial hypotheses.

The following conclusions can be drawn.

1. Placebo effect as a carrier of functional information. Placebo exerts pronounced modulating, mainly inhibitory, neurotropic effects. These effects are measurable and statistically significant compared to baseline and control waters.

2. Differentiation of placebo effects. An enhancing neurotropic placebo effect was observed on 9 variables; a weak inhibitory effect occurred on 8 variables; a moderate inhibitory on 10 variables; a noticeable inhibitory effect was recorded on 9 variables.

3. Effectiveness of discriminant analysis. Discriminant function analysis successfully distinguished between baseline, control waters, and test water (placebo). The statistical significance of this distinction was high (Wilks' $\Lambda = 0.219$; $\chi^2(56) = 127$; $p < 10^{-6}$).

4. Identification of key variables. 28 variables were identified as most significant in discriminating between groups. These variables included various EEG parameters (e.g., asymmetry, PSD in different frequency bands) and HRV measures.

5. Patterns of physiological changes. Several clusters of variables were identified that changed in response to the placebo intervention. These clusters suggest that the placebo effect influences various aspects of nervous system functioning.

6. Distinction from spontaneous rhythmic changes. 17 variables showed significant deviations from initial levels after consumption of control waters. These changes were interpreted as spontaneous rhythmic changes, not effects of the water itself. Placebo effects were noticeable above these spontaneous changes.

7. Individual differences. Although detailed results were not presented, the study suggests that personality traits (e.g., vagal tone and trait anxiety) may influence the placebo response.

8. Methodology. The study demonstrated the effectiveness of using distilled water as a carrier for the placebo effect when accompanied by verbal suggestion. The combination of EEG and HRV analysis proved effective in detecting subtle neurotropic changes.

9. Implications for future research. The study paves the way for further analyses of neurotropic effects of other informational factors, such as kyokushin karate kata, Sense and Cross fields, Christian prayer, and Holy water. Spoiler: the results have already been processed and are being prepared for publication.

10. Significance for clinical practice. The results suggest that placebo effects can have a significant impact on nervous system functioning. This highlights the potential importance of expectations and suggestions in a medical context.

11. Study limitations. The small number of participants (5 men) limits the generalizability of the results. Lack of detailed information about long-term effects or repeatability of the observed changes.

12. Perspectives. This study is the first in a series of planned experiments investigating various informational factors and their impact on neurotropic functions.

The study provides strong evidence that the placebo effect, induced through verbal suggestion, can elicit measurable and significant changes in nervous system functioning, which has potential implications for both scientific research and clinical practice.

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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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