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## SEXUAL DIMORPHISM IN RELATIONSHIPS BETWEEN OF PLASMA BILIRUBIN AND SOME NEURO-ENDOCRINE PARAMETERS

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### Summary

**Background.** Earlier we found that plasma uric acid, urea and creatinine causes modulating effects on neuro-endocrine parameters, as well as anxiety, but these effects are significantly different in men and women of different ages. The **purpose** of this study is to analyze the relationships between the plasma bilirubin level and some psycho-neuro-endocrine parameters in the same cohort. **Materials and Methods.** The object of observation were almost healthy volunteers: 31 males (24÷69 y) and 30 females, from among them 18 postmenopausal (48÷76 y) and 12 of reproductive age (30÷45 y). In basal conditions we determined plasma levels of bilirubin and adaptation hormones, estimated the severity of the trait and reactive anxiety, recorded the ongoing HRV and EEG. After 4 or 7 days, repeated testing was performed. **Results.** By building regression models with stepwise exclusion, it was found that in men plasma bilirubin upregulates the variability of  $\beta$ - and  $\alpha$ -rhythms as well as PSD of  $\beta$ -rhythm in T4 and Fp2 loci, but downregulates the variability of  $\theta$ -rhythm, PSD of  $\beta$ -rhythm in P4 and  $\delta$ -rhythm in T6 loci as well as the trait anxiety. The measure of determination is 42,6%. In postmenopausal women, bilirubin downregulates the PSD of  $\beta$ -rhythm in T6 locus, but upregulates the Testosterone plasma level, vagal tone as well as PSD of ULF and VLF bands HRV. The degree of determination of neuro-endocrine parameters is 59,2%. In women of reproductive age bilirubin upregulates the PSD of  $\beta$ -rhythm in T4 locus while downregulates the amplitude of  $\theta$ - and  $\beta$ -rhythms, PSD of  $\beta$ -rhythm in 5 loci, of  $\alpha$ -rhythm in 5 other loci as well as the Entropy of EEG in T5, P4 and C4 loci. The degree of determination of EEGs parameters is 97,8%. **Conclusion.** Plasma bilirubin has a modulating effect on psycho-neuro-endocrine parameters, but this effect is significantly different in men and women of different ages, which is due, apparently, to the influence of sex hormones on the expression of Ah receptors in neurons.

**Keywords:** plasma bilirubin, cortisol, testosterone, aldosterone, triiodothyronine, calcitonin, ongoing EEG, HRV, anxiety, men, women.

## INTRODUCTION

Earlier we found that plasma nitrogenous metabolites uric acid, urea and creatinine causes modulating effects on neuro-endocrine parameters, as well as anxiety, but these effects are significantly different in men and women of different ages [4-8,15,19].

The **purpose** of this study is to analyze the relationships between the plasma level bilirubin and some psycho-neuro-endocrine parameters in the same cohort.

## MATERIAL AND METHODS

The object of observation were employees of the clinical sanatorium "Moldova" and PrJSC "Truskavets' Spa": 31 males (24÷69 y) and 30 females, from among them 18 postmenopausal (48÷76 y) and 12 of reproductive age (30÷45 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 as a manifestation of maladaptation [4].

Testing was performed twice with an interval of 4 (in 11 men and 10 women; "Moldova") or 7 (in 10 men and 10 women; "Truskavets' Spa") days.

We determined the plasma levels of the Bilirubin (by diazoreaction using the Jedrashik-Kleghorn-Grof method [10]) as well as main adaptation hormones Cortisol, Aldosterone, Testosterone, Triiodothyronine and Calcitonin (by the ELISA with the use of corresponding sets of reagents from "Алкор Бю", XEMA Co. Ltd, and DRG International Inc).

The analyzers "Pointe-180" ("Scientific", USA), "Reflotron" (Boehringer Mannheim, BRD) and "RT-2100C" (PRCh) were used.

The levels of the trait and reactive anxiety estimated by STAI of Spielberger ChD [23] in modification of Khanin YL [18].

The state of the autonomic and central nervous systems was evaluated according to the parameters of heart rate variability [2,3,13,22] (software-hardware complex "CardioLab+HRV", KhAI-MEDICA, Kharkiv) and QEEG (hardware-software complex "NeuroCom Standard", KhAI MEDICA, Kharkiv).

In addition to routine parameters, Shannon's CE [21] Entropy of HRV and EEG were calculated [11,12,20]. See the previous articles for details [5,19].

Results processed by using the software package "Statistica 6.4".

## RESULTS AND DISCUSSION

Unlike urea and creatinine, for which we could not find appropriate receptors on PubMed and PMC resources, bilirubin realizes its effects through Ah-receptors [17], which are expressed, among other cells, also by neurons [9,14,16].

In men, bilirubin upregulates the variability of  $\beta$ - and  $\alpha$ -rhythms as well as PSD of  $\beta$ -rhythm in T4 and Fp2 loci, but downregulates the variability of  $\theta$ -rhythm, PSD of  $\beta$ -rhythm in P4 and  $\delta$ -rhythm in T6 loci as well as the trait, but not reactive anxiety. None of the registered hormones was included in the regression model. The measure of psycho-neural determination is 42,6% (Table 1 and Fig. 1).

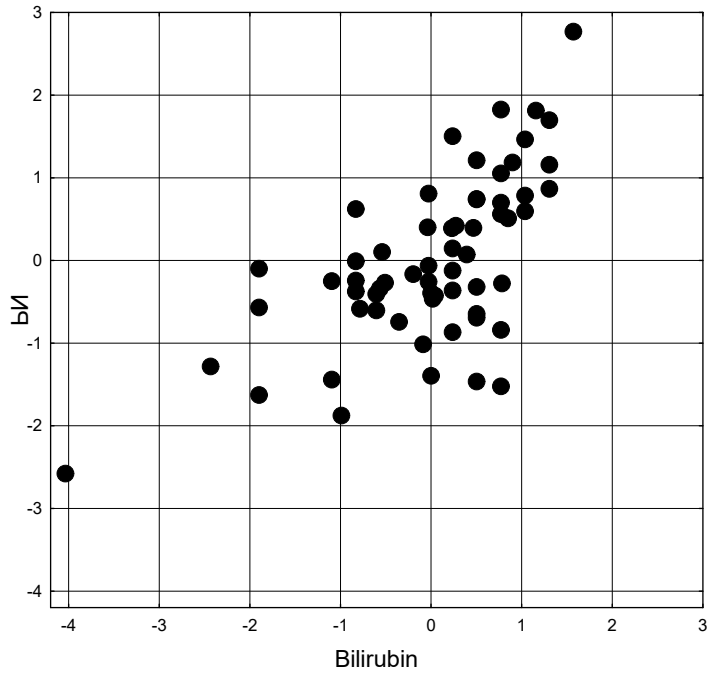
**Table 1. Regression Summary for Bilirubin plasma in Men**

R=0,653; R<sup>2</sup>=0,426; Adjusted R<sup>2</sup>=0,326; F<sub>(9,5)</sub>=4,3; p=0,0003

N=62		Beta	St. Err. of Beta	B	SE of B	t <sub>(52)</sub>	p-level
Variables	r		Intercept	18,0	3,4	5,25	10 <sup>-5</sup>
<b>Deviation-<math>\beta</math>, Hz</b>	<b>0,35</b>	0,239	0,117	1,593	0,777	2,05	0,045
<b>T4-<math>\beta</math> PSD, %</b>	<b>0,32</b>	0,279	0,152	0,075	0,041	1,84	0,071
<b>Fp2-<math>\beta</math> PSD, %</b>	<b>0,28</b>	-0,226	0,169	-0,062	0,047	-1,33	0,189
<b>Asymmetry-<math>\alpha</math>, %</b>	<b>0,23</b>	0,183	0,116	0,075	0,047	1,58	0,121
<b>Deviation-<math>\alpha</math>, Hz</b>	<b>0,21</b>	0,267	0,117	2,275	1,000	2,28	0,027
<b>P4-<math>\beta</math> PSD, <math>\mu V^2/Hz</math></b>	<b>-0,25</b>	-0,204	0,116	-0,0173	0,0098	-1,77	0,083
<b>T6-<math>\delta</math> PSD, %</b>	<b>-0,24</b>	-0,286	0,129	-0,047	0,021	-2,21	0,031
<b>Deviation <math>\theta</math>, Hz</b>	<b>-0,21</b>	-0,204	0,107	-1,438	0,753	-1,91	0,062
<b>Trait anxiety, points</b>	<b>-0,22</b>	-0,258	0,109	-0,139	0,059	-2,36	0,022

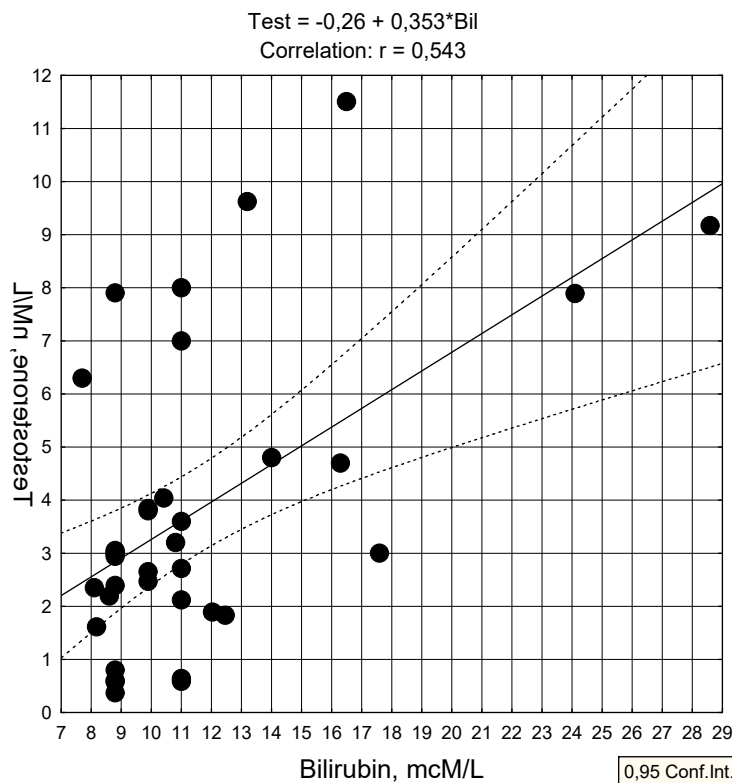
In postmenopausal women, bilirubin downregulates the PSD of  $\beta$ -rhythm in T6 locus (Table 2), but upregulates the Testosterone plasma level (Fig. 2), two HRV markers of vagal tone as well as PSD of ULF and VLF (Fig. 3) bands HRV. The latter, in turn, positively correlates with the level of testosterone (Fig. 4). The degree of determination of neuro-endocrine parameters is 59,2% (Table 2 and Fig. 5).

Our data is consistent with opinions that VLF band directly reflects both vagal and sympathetic tone [1] or vagal tone only [24] as well as saliva and plasma testosterone levels [25].

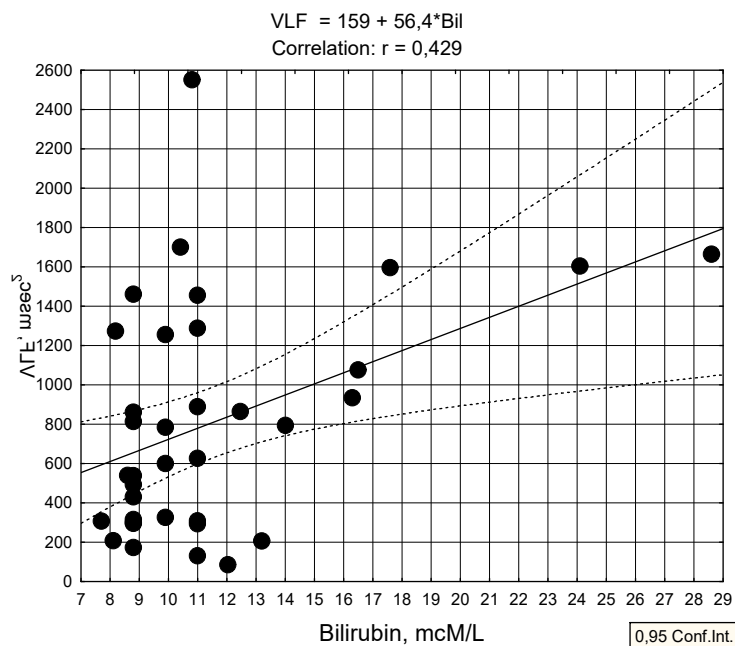


$R=0,653$ ;  $R^2=0,426$ ;  $\chi^2_{(9)}=31$ ;  $p=0,0003$ ;  $\Lambda \text{ Prime}=0,574$

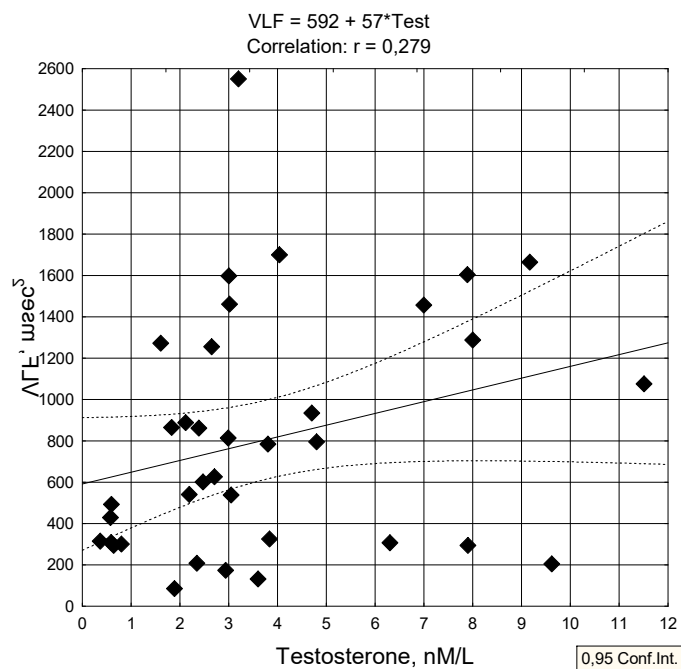
**Fig. 1. Scatterplot of canonical correlation between Bilirubin plasma (X-line) and Psycho-Neuronal parameters (Y-line) in Men**



**Fig. 2. Scatterplot of correlation between Bilirubin (X-line) and Testosterone (Y-line) plasma in postmenopausal Women**



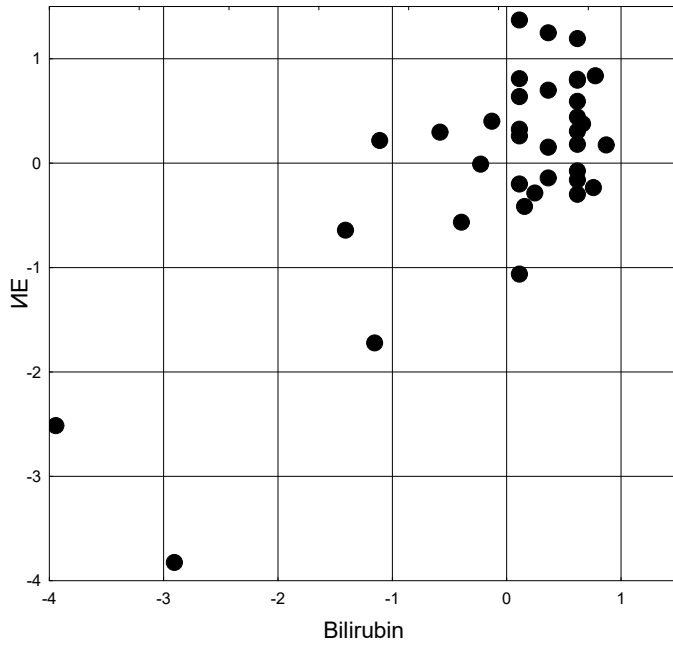
**Fig. 3. Scatterplot of correlation between Bilirubin plasma (X-line) and PSD of VLF band HRV (Y-line) in postmenopausal Women**



**Fig. 4. Scatterplot of correlation between Testosterone plasma (X-line) and PSD of VLF band HRV (Y-line) in postmenopausal Women**

**Table 2. Regression Summary for Bilirubin plasma in postmenopausal Women**  
R=0,770; R<sup>2</sup>=0,592; Adjusted R<sup>2</sup>=0,508; F<sub>(6,3)</sub>=7,0; p=0,0001

N=36		Beta	St. Err. of Beta	B	SE of B	t <sub>(29)</sub>	p-level
Variables	r		Intercept	9,64	2,54	3,80	0,001
<b>Testosterone, nM/L</b>	<b>0,55</b>	0,334	0,131	0,518	0,202	2,56	0,016
<b>ULF HRV PSD, msec<sup>2</sup></b>	<b>0,57</b>	0,406	0,143	0,0053	0,0019	2,84	0,008
<b>VLF HRV PSD, msec<sup>2</sup></b>	<b>0,43</b>	0,231	0,165	0,0018	0,0013	1,40	0,171
<b>MxDMn HRV, msec</b>	<b>0,44</b>	0,616	0,307	0,041	0,021	2,01	0,054
<b>TNN HRV, units</b>	<b>0,33</b>	-0,739	0,317	-0,938	0,403	-2,33	0,027
<b>T6-β PSD, μV<sup>2</sup>/Hz</b>	<b>-0,35</b>	-0,152	0,131	-0,0130	0,0112	-1,16	0,257

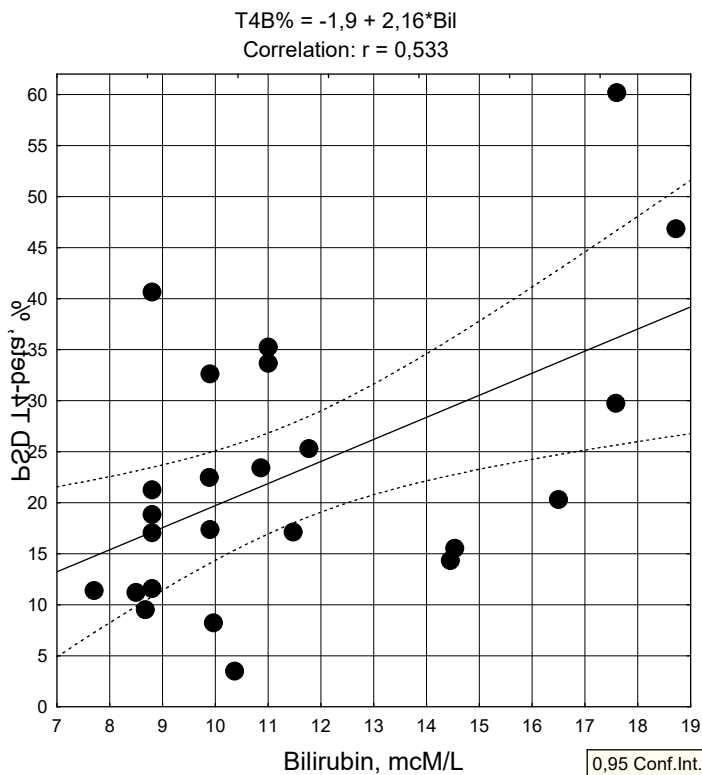


$R=0,770$ ;  $R^2=0,592$ ;  $\chi^2_{(6)}=28$ ;  $p=0,0001$ ;  $\Lambda$  Prime=0,408

**Fig. 5. Scatterplot of canonical correlation between Bilirubin plasma (X-line) and Neuro-Endocrine parameters (Y-line) in postmenopausal Women**

In women of reproductive age bilirubin upregulates the PSD of  $\beta$ -rhythm in T4 locus (Fig. 6) while downregulates the amplitude of  $\theta$ - and  $\beta$ -rhythms, PSD of  $\beta$ -rhythm in 5 loci (Fig. 7), of  $\alpha$ -rhythm in 5 other loci as well as the Entropy of EEG in T5, P4 and C4 loci (Table 3).

The degree of determination of EEGs parameters is 97,8% (Table 3 and Fig. 8).



**Fig. 6. Scatterplot of correlation between Bilirubin plasma (X-line) and PSD of beta-rhythm in T4 locus (Y-line) in premenopausal Women**

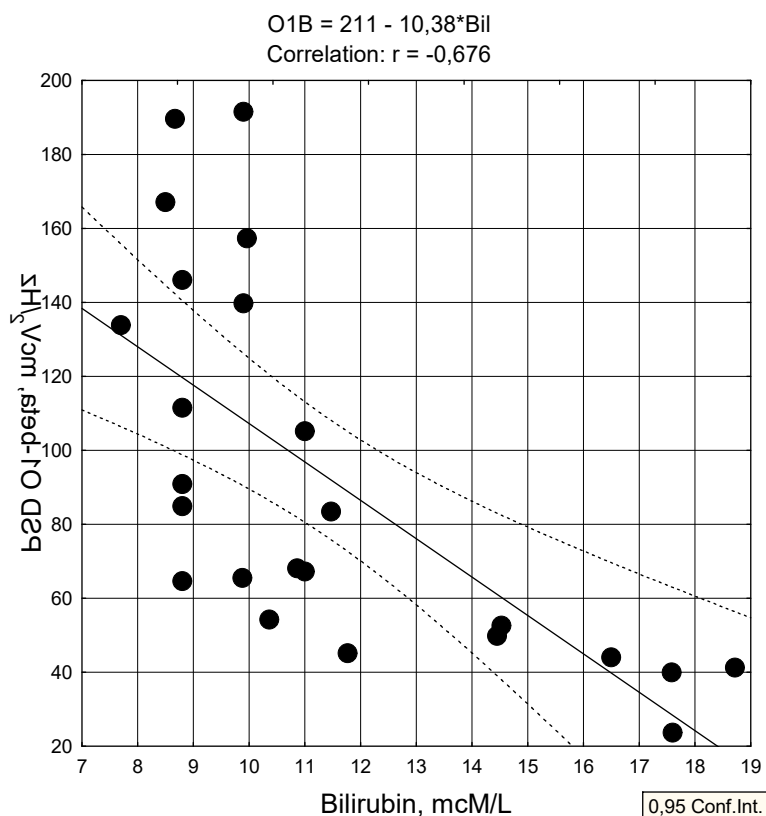
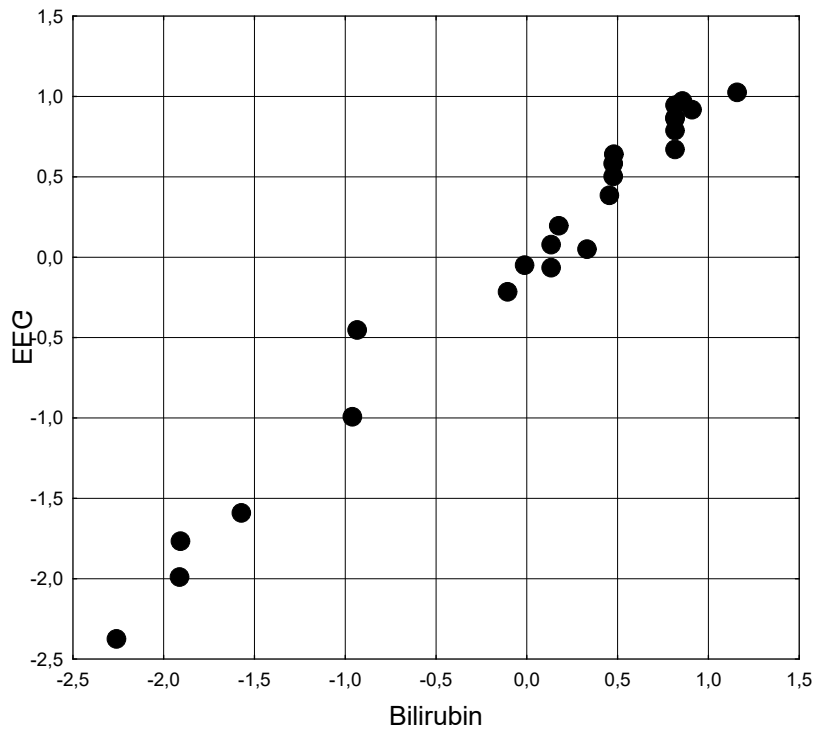


Fig. 7. Scatterplot of correlation between Bilirubin plasma (X-line) and PSD of beta-rhythm in O1 locus (Y-line) in premenopausal Women

Table 3. Regression Summary for Bilirubin plasma in premenopausal Women

R=0,989; R<sup>2</sup>=0,978; Adjusted R<sup>2</sup>=0,928; F<sub>(16,7)</sub>=19,6; p=0,0003

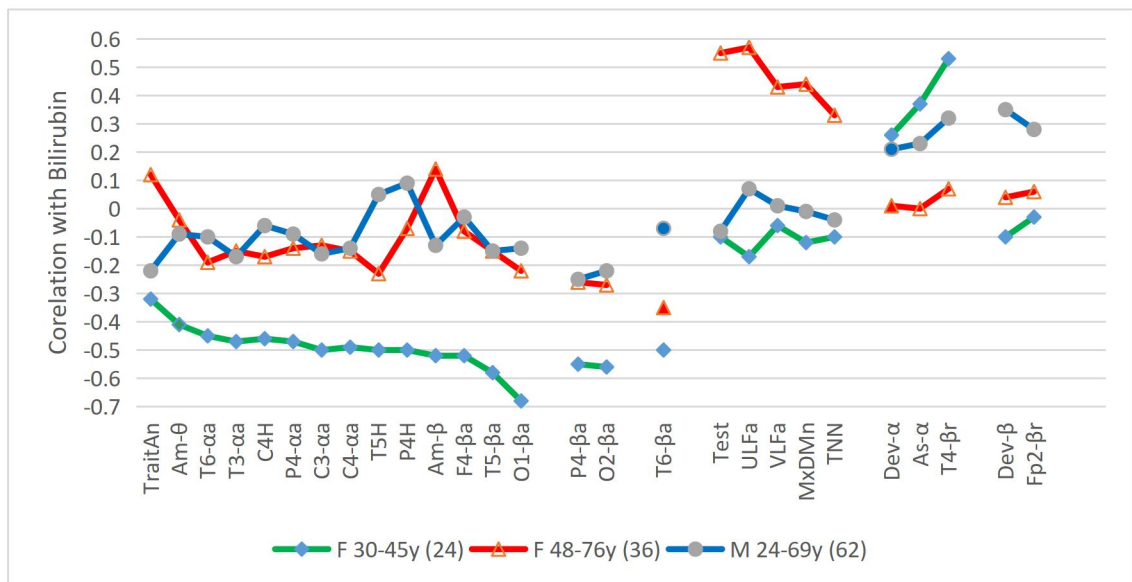
N=24		Beta	St. Err. of Beta	B	SE of B	t <sub>(7)</sub>	p-level
Variables	r		Intercept	25,6	2,24	11,5	10 <sup>-5</sup>
O1-β PSD, μV <sup>2</sup> /Hz	<b>-0,68</b>	-1,636	0,216	-0,1065	0,0141	-7,58	0,0001
T5-β PSD, μV <sup>2</sup> /Hz	<b>-0,58</b>	0,531	0,257	0,0550	0,0266	2,07	0,078
O2-β PSD, μV <sup>2</sup> /Hz	<b>-0,56</b>	-1,799	0,395	-0,1079	0,0237	-4,55	0,003
F4-β PSD, μV <sup>2</sup> /Hz	<b>-0,52</b>	-0,598	0,190	-0,091	0,029	-3,15	0,016
T6-β PSD, μV <sup>2</sup> /Hz	<b>-0,50</b>	-0,569	0,140	-0,0403	0,0099	-4,06	0,005
Amplitude β, μV	<b>-0,52</b>	2,840	0,415	2,980	0,436	6,84	0,0002
C3-α PSD, μV <sup>2</sup> /Hz	<b>-0,50</b>	-1,484	0,451	-0,0437	0,0133	-3,29	0,013
C4-α PSD, μV <sup>2</sup> /Hz	<b>-0,49</b>	-1,633	0,371	-0,0454	0,0103	-4,40	0,003
T3-α PSD, μV <sup>2</sup> /Hz	<b>-0,47</b>	2,298	0,360	0,1404	0,0220	6,38	0,0004
P4-α PSD, μV <sup>2</sup> /Hz	<b>-0,47</b>	2,548	0,462	0,0356	0,0065	5,51	0,0009
T6-α PSD, μV <sup>2</sup> /Hz	<b>-0,45</b>	-0,353	0,179	-0,0075	0,0038	-1,97	0,090
Entropy T5	<b>-0,50</b>	-0,384	0,101	-8,887	2,346	-3,79	0,007
Entropy P4	<b>-0,50</b>	0,384	0,211	10,30	5,666	1,82	0,112
Entropy C4	<b>-0,46</b>	-1,067	0,208	-27,16	5,283	-5,14	0,0013
Amplitude θ, μV	<b>-0,41</b>	-0,616	0,172	-0,700	0,196	-3,58	0,009
T4-β PSD, %	<b>0,53</b>	-0,209	0,105	-0,051	0,026	-1,99	0,087



$R=0,989$ ;  $R^2=0,978$ ;  $\chi^2_{(16)}=54$ ;  $p<10^{-5}$ ;  $\Lambda$  Prime=0,022

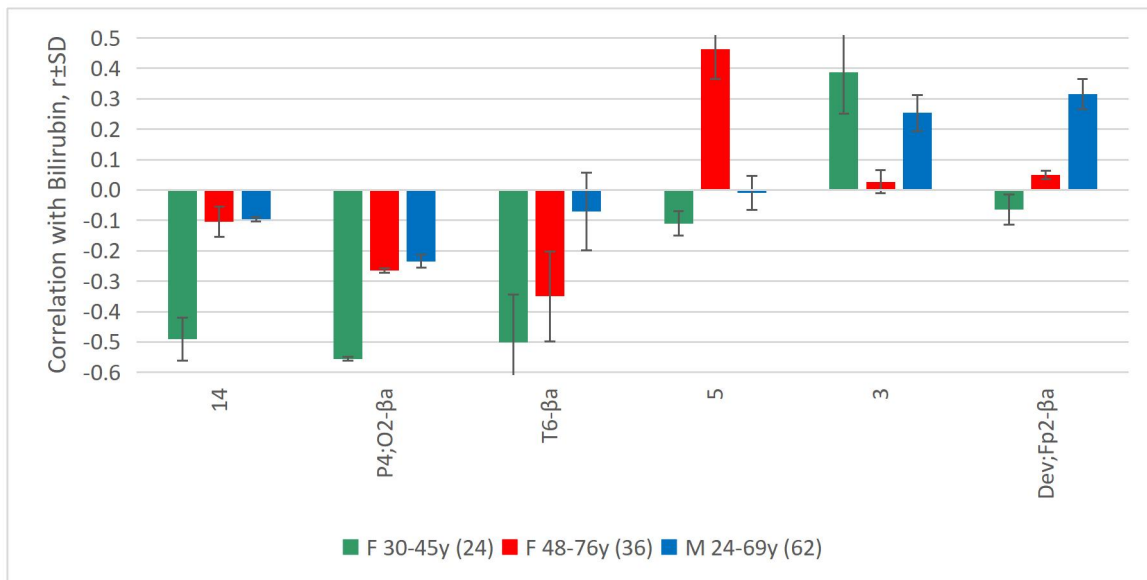
**Fig. 8. Scatterplot of canonical correlation between Bilirubin plasma (X-line) and EEGs parameters (Y-line) in premenopausal Women**

In order to visualize the strength and directionality of the relationships between plasma bilirubin levels and psycho-neuro-endocrine parameters at premenopausal and postmenopausal women as well as men, three profiles were created (Fig. 9).



**Fig. 9. Profiles of relationships between plasma Bilirubin and Psycho-Neuro-Endocrine parameters at premenopausal and postmenopausal Females as well as Males**

Next, the parameters were grouped into clusters (Fig. 10).



**Fig. 10. Clusters of relationships between plasma Bilirubin and Psycho-Neuro-Endocrine parameters at premenopausal and postmenopausal Females as well as Males. The number of variables in the cluster is given**

The first cluster of correlation coefficients, the largest in terms of the number of variables, reflects the inhibitory effect of bilirubin on neurons that generate  $\beta$ -,  $\alpha$ - and  $\theta$ -rhythms as well as on the level of trait anxiety specifically in women of reproductive age, while in postmenopausal women and men it has an inhibitory neurotropic effect bilirubin does not appear. This situation is probably due to the enhancing effect of **estradiol** on the expression of Ah receptors in neurons, the level of which in both postmenopausal women and men is insufficient to activate the expression.

The marginally significant inhibitory effect of bilirubin on  $\beta$ -rhythm generating neurons projecting to the parietal and occipital right loci in members of the other two cohorts is due, apparently, to a higher density of Ah receptors in these neurons, sufficient for the permissive effect of meager estradiol levels.

Significant inhibitory effect of bilirubin on  $\beta$ -rhythm generating neurons projecting to the posterior temporal right locus at postmenopausal women but not men is due, apparently, to the permissive effect of **estriol**. It is the last hormone, apparently, that is responsible for the enhancing effect of bilirubin on the testosterone level and vagal tone only in postmenopausal women.

The activating effect of bilirubin on the variability of the beta-rhythm and the activity of  $\beta$ -rhythm generating neurons projecting to the right prefrontal locus only in men is due, apparently, to the enhancing effect of testosterone on the expression of Ah receptors of these neurons.

The most problematic for us is the interpretation of the stimulating effect of bilirubin on the variability and asymmetry of the  $\alpha$ -rhythm and the activity of  $\beta$ -rhythm generating neurons projecting to the anterior temporal right locus at men and premenopausal women because at first glance it is impossible to identify common features for such different cohorts. This will be the subject of a separate analysis.

## ACKNOWLEDGMENT

We express sincere gratitude to administration of clinical sanatorium “Moldova” and PrJSC “Truskavets’ Spa” as well as TA Korolyshyn and VV Kikhtan for help in carrying out this investigation.

## ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out in accordance with positions of Helsinki Declaration 1975 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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