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ALLELIC POLYMORPHISM OF THE SEROTONIN TRANSPORTER AS A FORMATION FACTOR OF THE BEHAVIORAL COGNITIVE CONTROL IN THE YAKUTS

ABSTRACT

Allelic polymorphism of serotonin transporter 5-HTTLPR is connected with higher risk of vulnerabil-ity to the mental pathologies, which are associated with disorders in regulation of emotional behavior. However, the influence of this polymorphism on predisposition to disorders significantly differs in the different ethnic groups. The aim of our study is an exploration of the 5-HTTLPR effects on the change of theta-band spectral power in EEG in condition of recognition of the written emotional sentences in the Yakuts in comparison with the Russians. 78 healthy Yakutian students and 82 healthy Russian students participated in the study. In EEG experiment, the participants recognized a grammatical error in the Russian written sentences. The sentences contained a hidden condition, which was not clearly announced to participants: - some of sentences described unanimated objects, own anxiety of participant, anxiety of other persons, own aggression of participant or aggression of other persons. The probes of blood or buccal epithelium were taken in each participant for genetic analysis. It was revealed that the frequency of occurrence of the S-allele of the 5-HTT gene in the Yakuts was significantly higher (73%), than that in the Russians (39%). In EEG, the emotional sentences induced the higher amplitude of theta-band synchronization in comparison with the neutral sentences in all participants. The participants with the genotypes LS and SS showed essentially smaller differences in amplitude of EEG reaction after onset of sentences from different categories in comparison with the people with LL genotype. Our study supports the hypothesis that S- allele of 5-HTTLPR is associated with lower sensitivity to emotion-related stimuli, that could be connected with the risk of affective pathologies in people with such allele. Acknowledg-ment: Recording and processing of EEG was executed under financial support of the Russian Science Foundation, grant № 17-18-01019, «I and other – predictors and mechanisms of cooperative and competitive behavior». The collection of genetic probes was executive under support of the Russian Science Foundation, grant № 16-15-00128, «Structural features of gene SIRT1 as the basis for choose of personalized medicine therapy of depression».

Keywords: serotonin transporter (5-HTT), recognition of emotions, language comprehension, EEG, inter-ethnical comparison.

INTRODUCTION

Behavioral cognitive control is the complex of processes in the human brain, which is responsible for effective achievement of goals and adaptation to changeable environmental conditions [11]. According to the modern neuroscientific studies [8; 9], the behavioral control mechanism includes two contradicting to each other processes: an activation of goal-directed motions (so-called "activation control"), and an inhibition of motions, which are non-relevant to achievement of goals (i.e. "inhibitory control") [1]. Stop-signal paradigm (SSP) is the experimental method which was specially suggested for testing of balance between the activation and inhibitory processes in clinical norm and under different kinds of neurologic or mental disorders [5]. SSP experiment tests motor reactions of participants to the onset of several quickly appearance and disappearance stimuli. An examinee had to press one of two buttons quickly after the onset of different target signals. In some cases, the examinee had to suppress an movement, already begun, if after a target signal there was a stop-signal onset. The SSP technique is widely applied to testing patients with many kinds of behavioural pathologies, including Parkinson's disease, syndrome of children's hyperactivity, impulsive syndrome, etc.

Neurophysiological studies by means of EEG and fMRI techniques have shown that the activation of movements is connected with inclusion of the bottom-up processes arising in the parietal cortex. The movement inhibition is associated with top-down processes arising in the middle frontal cortex [8]. In EEG studies, the activation control is reflected in the dynamics of alpha/beta rhythm, whereas the inhibitory control is connected with the changes of delta/theta rhythm. Also, the EEG and fMRI indicators in the SSP conditions have the strong inter-personal variability depending on age, the anxiety level, and genetic features of healthy participants [7; 9].

The serotonin transporter (5-HTT) is the protein which mediates the re-uptake of serotonin from the synaptic cleft [11]. Several genetically defined modifications of this protein were detected in humans and animals. 5-HTTLPR on genetic site SLC6A4 is one of the allelic polymorphisms of the serotonin transporter. Among humans, this gene exists in two variants: "long" (L – allele) and short (S – allele) protein. Respectively, each person can have one of three genotypes: LL, LS, or SS [4]. In addition, the L- allele can be either active (La) or passive (Lg). Earlier, the numerous researches on animals and human clinical patients showed the association of an increased risk of many affective pathologies including anxiety disorder, depression, alcoholism, and predilection to suicide among people who have SS genotype [3; 4]. There was the assumption that the genetic analysis of this polymorphism can be used in preventive diagnostics of mental diseases which are related to the disturbance of self-checking of behavior. However, further researches generated some doubts about the efficiency of such an approach. In particular, it was revealed that the 5-HTTLPR polymorphism could have an opposite effect on vulnerability to mental disorder in representatives among Caucasian and Mongoloid ethnic groups. As it was shown in several independent studies, the S-allele is seldom among the population of Western Europe. This allele is associated with a higher risk of development of affective pathologies among the Europeans. On the contrary, the S- allele is widely spread among the Asian populations, including Japanese, Koreans, Mongols, and the Tuvinians. Among these Asian ethnic groups, S- allele is associated with lower vulnerability to the affective mental diseases [6; 10]. Thus, for the same mental disorder, the same genotype can appear as the factor, increasing the risk of disease and, in other ethnic groups, as the factor reducing the risk of this disease. By the present moment, the reasons of such an "invertation" of the genotype effect among different groups of people is still unclear. Is it bound to climatic conditions of life, features of education, economic factors, or to something else?

The aim of study: In this study, we compare the effect of the 5-HTTLPR allelic polymorphism on the behavioural mea-

sures and brain activity (EEG) in the experimental conditions of the Stop-signal paradigm among two ethnically different groups of healthy people (young Yakutian students who constantly live in Yakutsk, and young Russian students who constantly live in Novosibirsk). Firstly, we try to define whether the genetic differences in serotonin transporter structure influences the behavior and brain activity in the conditions of experimentally induced load to the system of behavioral cognitive control. Secondly, we do the comparative research on the 5-HTTLPR effects among two groups of healthy people differing who belong to different ethnical groups and residences.

METHODS

78 young and healthy Yakutian students of the Medical Faculty of the North-Eastern Federal University (age 20,1±2,3 years old, 30 men and 48 women) and 82 students of the Novosibirsk State University (age 22,1±3,4 years, 31 men and 51 women) participated in the study. All participants gave informed written consents prior to the experiment and filled out the questionnaire concerning their mental, or neurological diseases, or application of narcotic drugs and any other psychoactive substances. People with such diseases or those who used psychotropic drugs were excluded from the study. Besides, the level of general and emotional intelligence were estimated for all participants. IQ scores of the groups were matched as closely as possible based on their performance. The experimental protocol was approved by the ethical committee of the Institute of Physiology and Basic Medicine in accordance with the Helsinki Declaration of biomedical ethics.

The samples of blood and buccal epithelium for analysis of the 5-HTTLPR genetic polymorphism have been taken from all participants. The genetic analysis has been executed in the Institute of Cytology and Genetics of SB RAS, according to the method described in the paper of Savostyanov et al. [10].

The SSP version, earlier offered by A.N. Savostyanov with coauthors [9], was used for the EEG experiment. The participants played a computer game called “The Hunt”. The images of either a tank or a deer appeared randomly on the computer screen. In total number of 130 images with interstimulus intervals from 3 to 7 seconds were presented to each participant. Each image was demonstrated during 750 ms. The participant had to identify the image, to choose weapon (onions for a deer or anti-tank gun for a tank), and to press one of two buttons referred to a necessary weapon. If the participant managed to choose the weapon correctly before the image disappeared, their game account increased to one point (each time). If weapon was chosen incorrectly or if the choice took longer than 750 ms, one point was subtracted from the account. In 35 cases, the stop-signal (a red square in the center of the screen with the text, “STOP”) was presented after the emergence of target stimulus. Thus, two experimental conditions were suggested for each participant, “Go”, in case they needed to react quickly to a target signal, and, “Stop”, in case they needed to inhibit an already begun movement quickly.

The intervals between the emergence of target stimulus and the emergence of stop-signal were calculated individually. For this purpose, the average reaction time was defined during the first 30 presentations of target stimulus made without stop-signal. Delays between the target stimulus and the stop-signal were calculated in an equal proportion as 10%, 25%, 30% and 50% of the average reaction time. Respectively, for successful performance the participants had to level the balance of motor responses speed. They should not have reacted to a stimulus too quickly (since it increased the risk of pressing the button after stop-signal onset), and too slowly (since it increased the risk of missed pressing). Success at this game demanded difficult, balanced behavioral control taking into account several factors at once.

The average time of correct reactions in the “Go” condition, the percentage of missed pressing, the percentage of correctly and incorrectly chosen weapon, the percentage of correct inhibition after emergence of the stop-signal, the number of pressings before emergence of the stop-signal, and the number of pressings after emergence of the stop-signal were defined as the measures of behavioural indicators.

EEGs with the events markers were recorded from all the participants during the execution of linguistic task. EEGs were recorded with the help of the Brain Products amplifier, Germany, with bandpass range from 0,1 to 100 Hz, with a frequency of sampling of 1000 Hz. Among the group of Russians, the EEG records were carried out through 128 channels located according to the International 10-5% schema with the referent on Cz and grounding electrode on AFz. Among the Yakutian ethnic group, the EEG records were made through 64 channels located according to the 10-10% schema.

EEG-signals were processed by means of the EEGlab_toolbox [https://sccn.ucsd.edu/eeglab/index.php]. Under the pre-processing data, EEGs were filtered in the range from 1 to 40 Hz. Eye and motor artifacts were rejected by means of the analysis of independent components (ICA, [4]). Event-related spectral perturbations (ERSPs, [4]) were applied as the measure of brain activity connected to the tasks’ execution and for the revealing of genetic effects.

RESULTS

The significant differences between the frequencies of population distribution of the polymorphic alleles of the serotonin transporter gene were revealed among the groups of Russians and Yakuts. The frequency of La-allele was 51% among the participants of Russian group and 21% among the participants of Yakuts’ group, whereas the frequency of S-allele was 39% among Russians and 73% among the Yakuts. The frequency of Lg-allele was 6% among both groups. The significance of intergroup differences was estimated by the $\chi 2$ criteria.

The statistical significance of behavioural results was estimated independently for each of the chosen measures by means of one-way ANOVA with factors «group» (Yakuts or Russians) and «genotype» (LL, LS or SS). The main effect of «genotype» was highly significant for the percentage of correct pressings with the «Go» condition, $F(2, 150) = 5.09$; $p = 0.007$. The participants with the LL genotype have shown the reduced quality of task execution (82,7±1,3%) in comparison with the LS heterozygotes (87,4±0,9%), and with the SS genotype carriers (87,1±0,8%). Besides, the genotype had a significant influence on the indicator of general speed of reaction, $F(2, 150) = 4.31$; $p = 0.015$. The participants with LL genotype reacted to stimuli more slowly (575,2±5,9 ms) than those who carried the LS (554,4±4,2 ms) and SS (555,4±3,6 ms) genotypes. Thus, people at whom the S- allele has been revealed, both in homozygous (SS) and in heterozygote (LS) positions, have shown the higher speed of reaction and greater success at task-execution in comparison with the LL people. Significant values of the factor «group» without interaction with a factor «genotype» have been revealed for the percentage of correct pressings, $F(1, 150) = 4.88$; $p = 0.029$, (Yakuts have 88,0±1.4% and Russian have 84,3±0,9%) and also for the indicator of missed pressings, $F(1, 150) = 6.55$; $p = 0.012$, (Yakuts have 8,9±1,3% and Russians have 12,9±0,8%). Thus, the Yakutian participants have shown significant, though not too essential, advantages in comparison with Russian participants on measures of motor control, which have not been directly connected with the 5-HTTLPR polymorphism.

In general, the EEG patterns in both SSP-conditions corresponded to what was received in our earlier study [9]. The spectral power increase (synchronization) in the interval of 100-1000 ms after a target stimulus onset in the 1-7 Hz frequency range with an amplitude maximum in visual cortex was revealed in the «Go» condition. Also, during 300-1500 ms interval and at 8-12 Hz frequency range the spectral power decrease (alpha-desynchronization) was revealed in frontal and parietal cortical areas. In the central (motor) cortex, the desynchronization in the frequency range of beta-band (12-20 Hz) was obtained, which directly preceded button pressing.

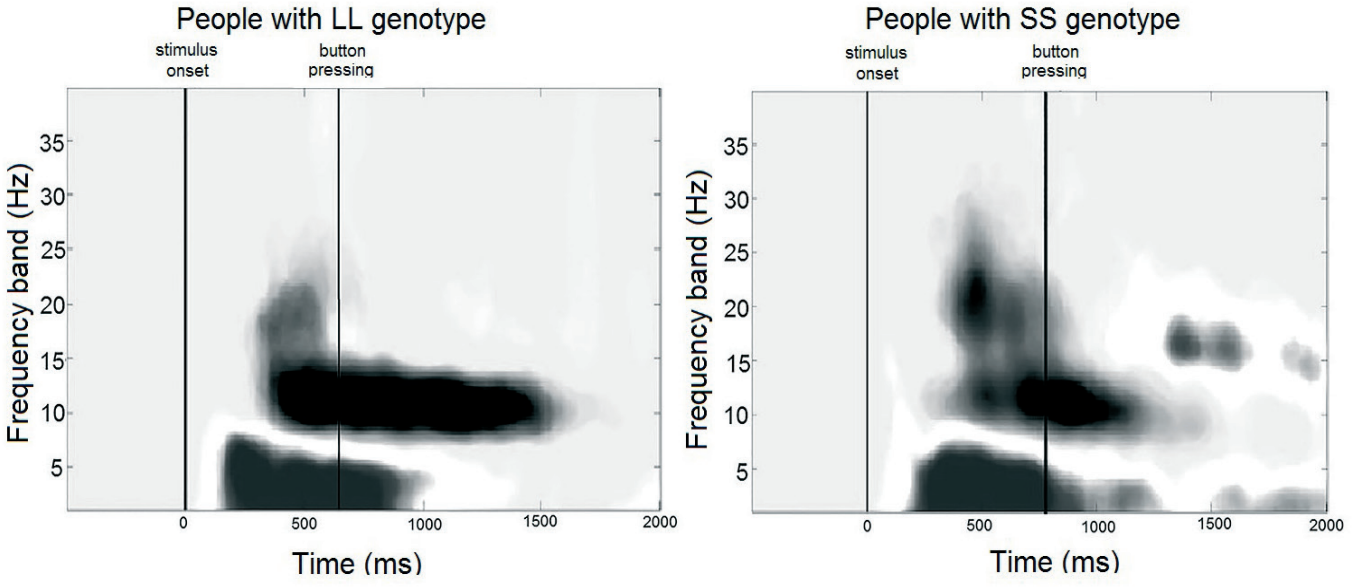

Figure 1. The differences in EEG responses in the «Go» condition of SS between the people with LL genotype (left) and SS genotype (right). A first vertical line reflects the moment of target-stimulus onset on the computer screen, second vertical line represents the moment of button pressing. The plot of event-related spectral perturba-tion (ERSP) shows values averaged among the people with LL (left panel) and SS (right panel) genotype. The duration of alpha-desynchronization is longer among the people with LL genotype than that among the SS people.

In the «Stop» condition, the amplitude of alpha and beta responses was reduced in comparison with the «Go» condition, but the additional high-amplitude synchronization in slowly-wave EEG ranges (delta and theta) was shown. Comparison of two genetically different groups of participants was carried out by means of the nonparametric bootstrap method (see the Figure 1). It was shown that the participants with LL genotype had longer (about 1500 msecs) and higher amplitude of alpha-desynchronization in comparison with the carriers of the LS and SS genotypes, both in the «Go» and «Stop» conditions of the SSP. Correlation analysis revealed that the latency of alpha-desynchronization in both experimental conditions negatively correlates with the quality of task execution ($r = -0,56$; $p = 0,045$) and the time of task execution ($r = -0,73$; $p = 0,003$), i.e. smaller latency corresponded to better and quicker task execution. Beta rebound, i.e. increase in beta-power after the task finishing, have been found in the 15-20 Hz frequency range among the carriers of the LS and SS genotypes only, but not in the LL carriers.

DISCUSSION AND CONCLUSION

Thus, we revealed that the S-allele of the 5-HTTLPR polymorphism is more widely spread among the Yakutian population in comparison with Russians and, vice versa, L- allele is spread more widely among Russians, that completely corresponds to the results which were received earlier by the comparing other Caucasian and Mongoloid populations [6; 10]. It is also revealed that among both Russians and Yakuts, people with S- allele showed significantly higher abilities to control the difficult behavior in the conditions of time deficit. In addition, Yakuts have shown better abilities to the sensory-motor task execution in the SSP conditions, in comparison with Russians, which directly are not connected with 5-HTTLPR polymorphism. Theoretically, it could be caused either by living conditions or some other genetic factors which were not researched by us. EEG shows that S- allele carriers have demonstrated shortened and lowered amplitude responses in alpha-band. It was also connected with the quality of motor control.

In the introduction to this article, we mentioned that S-allele is connected with higher vulnerability to affective disorders among the European population and with lower vulnerability to such violations among the Mongoloid populations. With the help of the results given in our study, it is possible to conclude that S-allele improves an ability to the behavioral control in the conditions of time deficit. We assumed that the high frequency of occurrence of this allele among Yakuts can be connected with the fact that it is the adaptive factor in those climatic conditions which assume the need of fast estimates of external events and executions of decisions. It is also possible to note that S-allele carriers have shown the decreased stability of attention (in case of the tasks execution that it is reflected in the alpha-band dynamics). It can be the reason of the violations arising among such people in environmental conditions, which are not connected with time deficit for decision-making, but with requiring the long and steady concentration of attention.

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ALA54THR POLYMORPHISM OF THE *FABP2* GENE AND METABOLIC SYNDROME IN THE YAKUT POPULATION

ABSTRACT
The metabolic syndrome represents complex of the metabolic risk factors connected with increase in prevalence of diabetes and cardiovascular diseases. Each component of metabolic syndrome to some extent has communication with heredity that demonstrates that genetic factors can have significant effect on pathogenesis of this syndrome. In researches among some populations the association of polymorphism Ala54Thr of gene of *FABP2* (rs1799883) with metabolic violations was shown. We analyzed association of allelic rs1799883 options (*FABP2*) with metabolic syndrome and its components at representatives of the Yakut ethnic group (on self-determination) from Berdigestyakh village of the Gorniy region of Republic Sakha (Yakutia). All surveyed people the written informed consent to participation in research. The program of research included screening by uniform technique on detection metabolic risk factors of chronic noncommunicable diseases. Polymerase chain reaction in real time was carried out in the CFX96 system of production Bio-Rad. Tests and primers were developed by means of the Beacon Designer 8 program from PREMIER Biosoft. From 228 participants of 42% had the increased level of blood pressure, 9,7% — the reduced level high density lipoproteins, 5,8% — raised triglycerides, 22,4% — fasted hyperglycemia, 56,8% — abdominal obesity, 16,8% — metabolic syndrome by IDF criteria (2005). G polymorphism of Ala54Thr *FABP2* (71%) are characteristic of the vast majority of representatives Yakut population allele carriage. Frequency of GG genotype was 42,1% (95% CI 35,9-48,6%), AG — 57,9% (95% CI 51,4-64,1%). The association of genotype AG with abdominal obesity was established at OR 1,7 (95% CI 1,01-2,99). Taking into account prevalence in this group of the population of such metabolic disturbances as obesity and the increased level of blood pressure, and also the growing incidence of diabetes type 2, it is necessary to continue search of genes of predisposition to these diseases.

Keywords: *FABP2* gene (rs1799883), Ala54Thr polymorphism of the FABP2 gene, metabolic syndrome, abdominal obesity, Yakut population.

INTRODUCTION

The metabolic syndrome is complex of the metabolic risk factors connected with increase in prevalence of diabetes and cardiovascular diseases [8, 12]. Each component of metabolic syndrome to some extent has communication with heredity that demonstrates that genetic factors can have significant effect on pathogenesis of this syndrome [9, 12, 15]. The gene of the protein connecting fatty acids in intestines (*FABP2*) participates in regulation of capture and transfer of long-chain fatty acids [5]. Polymorphic options of gene *FABP2* (rs 1799883) can exert impact on concentration of lipids in blood plasma and their intracellular transport [6]. The result of researches, conducted among northern populations was shown that lipid metabolism plays key role in effective adaptation to conditions of cold climate [1, 3]. The Republic of Sakha (Yakutia) belongs to terri-