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CONNECTION OF THE EEG REACTIONS IN THE CONDITION OF RECOGNITION OF EMOTIONAL LEXICA IN THE YAKUTS WITH ALLELIC POLYMORPHISM OF THE SEROTONIN TRANSPORTER

ABSTRACT

Allelic polymorphism of serotonin transporter 5-HTTLPR is connected with higher risk of vulnerability 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 between different ethnic groups. The aim of our study is exploration of the 5-HTTLPR effects on the change of theta-band spectral power in EEG in the condition of recognition of written emotional sentences among Yakuts in comparison with Russians. 78 healthy Yakutian students and 82 healthy Russian students participated in the study. In EEG experiment, the participants were to find grammatical errors in the sentences written in Russian. These sentences contained implicit conditions: some of the sentences described unanimated objects, anxiety of participants, anxiety of other people, participants' aggression, or aggression of other people. The probes of blood or buccal epithelium were taken from each participant for genetic analysis. It was revealed that the frequency of occurrence of S-allele of the 5-HTT gene was significantly higher among Yakuts (73%) than that among Russians (39%). According to EEG, the emotional sentences induced higher amplitude of theta-band synchronization in comparison with the neutral sentences among all the 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 LL genotype carriers. Our study supports the hypothesis that S- allele of 5-HTTLPR is associated with lower sensitivity to emotion-related stimuli. It could be connected with the risk of affective pathologies among people with such an allele.

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

INTRODUCTION

Affective pathology is the group of mental disorders such as the depressive disorder, anxiety disorder, autism, alcohol or drug addiction, which accompanied by the dysfunctions of regulation of human emotional behavior. High risk of affective pathology in the modern society makes the elaboration of methods important for early diagnostic and prevention of such diseases in their initial stages. One of the indicators reflecting the increased risk of vulnerability to affective pathology among non-clinical subjects is the inability to distinguish emotional states of other people and difficulty in relevant expression of their own emotional states [1].

The electroencephalogram (EEG) recorded in the conditions of recognition of external stimuli reflects an individual personal ability to recognition of emotions [2; 9]. EEG can also serve as the technique of assessment of the vulnerability to affective pathology [3]. Stimuli-induced synchronization in theta (4-8 Hz) frequency band is one of the most important EEG indexes associated with emotional regulation. Theta-synchronization (or task-induced increase in spectral power) reflects the involvement of limbic structures to the process of stimulus recognition, assessment, and decision-making [2; 9]. The personal differences in the amplitudes and cortical topology of theta rhythm serve as one of the main markers of affective pathology.

The different kinds of emotion-related photographs (including facial photographs) are usually used as the external stimuli for induction of different emotional states [2; 9; 18]. Another approach consist of demonstration the samples of emotionally expressive speech to the participants [17]. The application of oral or written speech allows to simultaneously manipulate many modalities of stimulus and changing the cognitive and emotive effects to the participants. In particular, speech stimulation allows to direct the emotional loading of stimulus, or to the participants themselves, or to other people. It gives us the opportunity to use personal orientation of stimulus as a special experimental modality. Therefore, the method of speech stimulation can significantly improve the traditional approach of the facial stimulation for search for the neurophysiologic correlates of emotions perception.

One of the directions of modern science is the search for genetic markers connected with specific features of healthy people or with the risks of vulnerability to various neurologic or mental pathologies. Most often, the polymorphic variants of alleles of one of the brain neurotransmitter systems are used as such markers [6]. The serotonin (5-HT) system is strongly associated with the regulation of all aspects of emotional behavior. This is the reason of high concentration of researchers who are studying the role of allelic polymorphisms of this system in the formation of personal features of emotion perception [13]. The serotonin transporter (5-HTT) is the protein which mediates the re-uptake of serotonin from synaptic cleft [11]. Several genetically defined modifications of this protein were identified among humans and animals. One of allelic polymorphisms of the serotonin transporter is the 5-HTTLPR on genetic site SLC6A4, localized in the 17th chromosome. Among humans, this gene exists in two variants: "long" (L- allele) and short (S– allele). Respectively, each person can have one of three genotypes – LL, LS or SS. In addition, the L- allele can be either active (La) or passive (Lg). The association of 5-HTTLPR polymorphism with an anxiety disorder, depression, and bipolar disorder, and also with sensitivity to antidepressants and suicide was shown in many different studies [7; 8; 5]. However, the connection of serotonin transporter with the individual features of emotional behavior among healthy people still remains unclear. In literature, there are opposite points of view about the role of 5-HTT polymorphisms in regulations of behavior [15; 16].

According to one of hypothesizes for explanation of these differences, the behavioral effects of genotype can be modified by socio-cultural factors in essential degree, in particular, by the ethno-social specificity of people [12]. Earlier, we have carried out the comparison of the effect of 5-HTTLPR among the groups of Tuvinian and Russian participants. It has been shown that the S- allele is associated

with high anxiety level among Russians, but not among Tuvinians [14]. In this study, we check the effect of genetic polymorphism of the serotonin transporter in EEG reactions in theta frequency band among healthy young Yakuts and Russians in the conditions of recognition of the emotional and personal-oriented sentences written in Russian.

The aim of study consists of the comparison of the effects of 5-HTTPLR allelic polymorphisms on the individual abilities to recognition of emotional and personal-oriented lexis among the groups of healthy Yakuts and Russians.

THE PARTICIPANTS AND METHODS

78 young healthy Yakutian students of the Medical Faculty of the North-Eastern Federal University (age 20,1±2,3 years, 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 the informed written consent priors 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 using psychotropic drugs were excluded from the study. Besides, the level of general and emotional intelligence were estimated for all the participants. The groups were matched as closely as possible according to their IQ scores. 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 or buccal epithelium for analysis of the 5-HTTLPR genetic polymorphism have been taken from all the 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 Lesch et al. [10].

During the EEG experiment, 200 sentences, written in Russian, were randomly presented to each of the participants. Half of the sentences contained syntax errors, another half was grammatically correct. All the sentences were partitioned into 5 categories: "neutral sentences about unanimated objects", "participants' own anxiety" (sentences are taken from the Spielberger 's STAI), "others' anxiety" (in sentences from the category "own anxiety", 1st person pronouns are replaced with 3rd person pronouns), "participants' own aggression" (sentences are taken from the Buss-Perry aggression questionnaire), "others' aggression" (in sentences from the category "own aggression", 1st person pronouns are replaced with 3rd person pronouns). Participants were not informed about separation of sentences into several emotional-related categories before the experiments. Sentences appeared on the computer screen randomly during time period from 3 to 5 seconds. The task for the participant was to define existence of syntax errors in the presented sentences.

EEG with the events markers was recorded from all participants during the execution of linguistic task. EEG was 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. For the Russian group, the EEG record was carried out through 128 channels located according to the International 10-5% schema with the referent on Cz and grounding electrode on AFz. For the Yakutian group, the EEG record was 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 data pre-processing, EEG was 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 a measure of the brain activity connected to the task's execution and for the revealing of genetic effects.

ERSPs have been calculated for each participant on each EEG channel. Based on our previous results [9; 17;], the frequency range in theta band (4-8 Hz) during the time interval from 0 to 300 ms after the sentence's onset was used for identification of genetic effects on brain activity, because this index reflects the degree of the emotional pressure which was experienced by the participants during stimulus recognition. The repeated-measures ANOVA with the factors "sentence's category" (five emotionally differed categories), "group of participants" (Yakuts or Russians), "saggitaly" (the EEG channels oriented between frontal and posterior regions), "laterality" (the EEG channels oriented between left and right regions), and "genotype" (three genotypes of LL, LS or SS) with the correction on multiple comparisons was applied for assessment of the statistical significance of the effects.

RESULTS

The significant differences in the frequencies of population distribution of the polymorphic alleles of the serotonin transporter gene was revealed among the groups of Russians and Yakuts. The frequency of La-allele was 51% among Russians and 21% among Yakuts, whereas the frequency of S-allele was 39% among Russians and 73% among Yakuts. The frequency of Lg-allele was 6% for both groups. The significance of intergroup differences was estimated by the χ^2 criteria.

The amplitude of the theta-response after appearance of non-emotional sentences about unanimated objects was significantly lower in comparison with the responses to other categories of sentences among all the participants, regardless of their nationality and genotype. This effect was highly significant: $F = 8,48$; $p < 0,0001$, and this indicates the connection between theta responses and emotional content of speech. For the theta-synchronization, the main effect of "group" factor was significant: $F = 5,01$; $p = 0,027$. The Yakutian ethnic group showed higher amplitude of theta-synchronization (1,7±0,2) in comparison with the Russian group (1,2±0,1). This could be interpreted as bigger tendency of Yakuts to emotional response on onset of the anxious and aggressive sentences. Also, the significant interaction of factors "group" to "sentence category", $F = 2,19$; $p = 0,013$, was revealed. Among the Yakutian group, the amplitude of responses to sentences about participants' own aggression and others' aggression did not differ (respectively, 1,1±0,1 and 1,0±0,1), whereas among the Russian group, the response to sentences about others' aggression (0,3±0,1) was significantly lower than the response to sentences about participants' own aggression (0,5±0,1).

The main effect of genotype was non-significant for both groups of participants ($p = 0,6$). However, among both of groups the significant interaction of factors "sentence's category" to "genotype", $F = 2,32$; $p = 0,022$, was revealed (see Figure 1). The carriers of the LL genotype showed a differentiated pattern of the EEG response to the different categories of sentences. Among such people, the EEG responses to all five categories of sentences were different in theta-synchronization amplitude. On the contrary, among the SS genotype carriers, the EEG responses to different types of sentences were almost the same in the amplitude of theta response, and the LS heterozygotes showed differences in responses to neutral (objects) and emotional (all remaining categories) sentences only, but did not show any differences in the responses to the various categories of emotional sentences. The interaction of factors "genotype" and "ethnic group" was not revealed.

DISCUSSION AND CONCLUSION

In general, our results confirm the hypothesis that S- allele of the 5-HTTLPR is connected with weak ability to recognize other people's emotions [8; 16]. In this case, it worsens the understanding of emotional load of written speech. Yakuts and Russians have shown the identical influences of genotypes on the EEG reaction, but S-allele is found among Yakuts significantly more often than the same among Russians. Besides, it was revealed that there are the number of features of Yakuts' brain activity which distinguishes them from Russians but cannot be explained distinctly by the 5-HTTLPR influence. It is also possible to assume that the lower sensitivity to the speech emotional load in different social conditions can have a different influence on behavior, which explains the different

connection of a genotype with the risk of pathological development among the Caucasian and Mongoloid populations.

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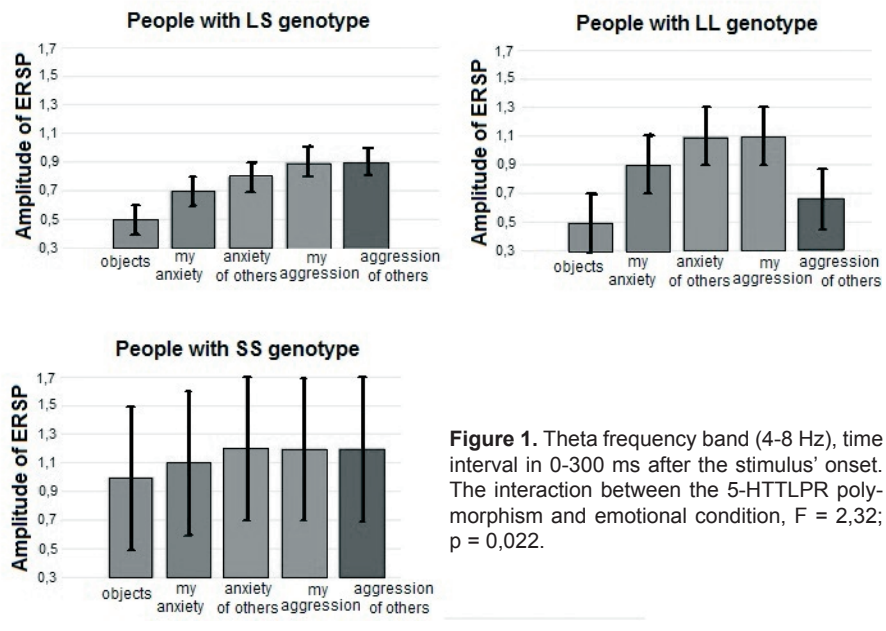

Figure 1. Theta frequency band (4-8 Hz), time interval in 0-300 ms after the stimulus' onset. The interaction between the 5-HTTLPR polymorphism and emotional condition, F = 2,32; p = 0,022.

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GENETICS OF VILYUI ENCEPHALOMYELITIS

ABSTRACT

Viliuisk encephalomyelitis (VE) is a neurodegenerative disease with unknown etiology in development of which genetic factors have significant role. Study of HLA markers and other genes of immunity and analysis of exom sequencing in VE patients revealed features of the Yakut genome, predisposing to immunity dysfunction and functional insufficiency of proteolitic and phosphatase activity. In extreme environmental conditions these features may lead to dystrophic process development in the brain and distinguish type of encephalopathy as basis of VE pathogenesis.

Keywords: Viliuisk encephalomyelitis, genes of immunity, human exom, DNA sequencing.

INTRODUCTION

Viliuisk encephalomyelitis (VE) is the regional pathology of Republic Sakha (Yakutia). Study of etiology and pathogenesis of this disease since difficult nature remains subject of fundamental medicine.

At present time VE consider as primary chronic form of disease, in which a patient experience physical weakness of nervous system due to the gradual degradation of neural circuits and the death of neurons. Disease may have form of encephalopathy with stable, steady flow and minimal degrees of motor and cognitive impairments. However, in some of these patients undergone extreme physical stress (undercooling, trauma, childbirth), external factors can provoke acute inflammation of the brain (encephalitis) with a local immune response and development of a clinical picture of an acute or subacute form of the VE with possible fatal outcome [4]. Patients who survive acute inflammation develop a chronic process typical for all patients with VE. The nature of the primary neurodegenerative process in VE remains unresolved. Currently, the working hypothesis is a violation of the control function of intracellular autophagy of the neuron, inducing atrophy of tissue and spongios of the brain. The reason of which may be a violation of the molecular mechanisms that control this function. The study of the genetic component in the etiology and pathogenesis of the disease is an important aspect of the disclosure of the molecular nature of VE pathology. In recent years, modern methods of molecular genetics are being used to solve this problem.

1. Population-genetic studies of VE

The disease is known to be endemic (the focus of the disease is limited by the Vilyui river region) and afflicts only Sakha people. The disease is sporadic, group cases of the disease are not observed, but generic connections are traced. The involvement of heredity in the development of the disease was confirmed by population-genetic studies on the material of a mass neurological survey of the population of the districts of the Vilyui basin for 1969-1977 in the works of Goldfarb LG, et.al. [6]. Segregation analysis (the ratio of patients among siblings) showed the absence of a monogenic type of autosomal recessive inheritance, but does not exclude the inheritance of more than one gene, the mutual action of which predisposes to the disease. To analyze the contribution of the genetic component and environmental factors to the pathology of the VE, the Falconer-Edwards mathematical model was used to calculate the coefficient of heritability (H). The coefficient of heritability of the phenotype of the disease for relatives of the 1st degree of kinship was 22.14% in the Vilyui district and 28.94% in the other districts of the Vilyui basin [6]. This means that the disease of VE among the Yakut population is due to the genetic component by 22-29% and due to the action of external environmental factors by 71-78%. Environmental factors make a significant contribution to the development of encephalitis in patients.

2. Investigation of immunity genes

Genetic studies of VE have been initiated with immunity genes. In the work of V. V. Fefelova (1996) analysis of HLA class 1 markers using serological reactions showed a slight statistically significant increase of the HLA-b15 variant in patients with VE [7].

Genotyping of alleles of HLA 2 class (-dp, -dq, -dr) on variants of DQA1 gene was carried out in patients with VE, which revealed an ethnic difference in frequency of allele 0301 ($p < 0,05$) between patients of Yakut and European origin. At the same time, the frequency of DQA1'0301 in patients with VE was higher than in healthy Yakut patients [9]. This gives grounds for talking about the participation of immunity genes in the development of the pathogenesis of VE disease.

At a next stage of research to search for new immunity candidate genes predisposing to the VE, 7 inflammatory genes were analyzed. These are the genes of the chemokine receptors *CCR2 / CCR5,* interferon gamma, interleukins 4, 6, 10 and the stromal factor (CDF) and cytokine Rantes [8]. 17 single nucleotide substitutions (SNPs) were analyzed. As