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RESEARCH ARTICLE

Associations between genetic factors in individualization of visual perception and components of event-related potentials during assessment of emotional visual stimuli (scenes) with distinct second-order features [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: The aim of this paper is to investigate the associations between polymorphisms in the *BDNF*, *COMT*, and *HTR2A* genes with peculiarity of visual perception. In particular, how the carriers of different genotypes of Indicated genes emotionally evaluating visual scenes with distinct second-order features (images modulated by contrast) and how corresponding process is reflected in event-related brain activity (ERP).

Methods: The study involved students who underwent PCR-based genetic analysis with the release of *BDNF*, *COMT*, and *HTR2A* genotypes. Participants were asked to emotionally assess the specific stimuli – visual scenes that were generated from contrast modulations. At the same time the EEG were recorded using a 128-electrodes system. The average frequency of responses and ERPs for different emotional evaluations (negative, neutral and positive) were analyzed.

Results: The study showed the *BDNF* Val/Val polymorphism was associated with the increase in the P2 amplitude in the occipital regions compared to the Val/Met genotype regardless of emotional

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evaluation. The *COMT* Met/Met genotype polymorphism associated with the increase of N170 negativity in the occipital regions during evaluation task. The *HTR2A* polymorphism A/A associated with increase in the P1 amplitude when positive or negative assessment were chosen, and decrease of later positive peak when neutral evaluation was chosen.

Conclusions: The results suggested that emotional evaluation and recognition of visual scenes with distinct second-order features, as well as various strategies for processing visual information, reflected in amplitude and latency of different ERPs components and associated with the different genotypes of *BDNF*, *COMT*, and *HTR2A* genes. The indicated interconnections can act as genetic basis of individualize the mechanisms of visual perception.

Keywords

Second-order visual features, *BDNF* gene, *COMT* gene, *HTR2A* gene, visual scenes, visual perception, emotions, event-related potentials, emotional assessment

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Introduction

Despite the fact that at this stage of evolution, the human visual system is the main channel for receiving information that performs complex processes of encoding and decoding stimuli, the mechanisms for recognizing and categorizing visual images still remain under-investigated (Babenko *et al.*, 2011; Graham, 2011; Wilson & Gelb, 1984). In particular, second-order visual features – non-local characteristics of the perceived image, which including various options for contrast, orientation, and spatial frequency – are of special interest to human's visual system researchers (Babenko *et al.*, 2011; Babenko *et al.*, 2016). These features are image regions characterized by spatial heterogeneities of brightness gradients – the first-order characteristics. These heterogeneities are distinguished by the so-called second-order filters, which detect regions with spatial modulations of contrast, orientation, and spatial frequency in the images. First-order visual mechanisms form the basis for subsequent spatial grouping. This is a multi-channel system that performs local analysis of the orientation of the brightness gradients at various spatial frequencies. Second-order visual mechanisms detect spatial changes and represent a certain set of filters.

A number of experimental studies demonstrated that second-order visual mechanisms are selective towards modulations of contrast, orientation (surface curvature) and spatial frequency (depth) and have different cortical localization. The search for second-order stimuli is pre-attentive (Yavna & Babenko, 2012; Yavna *et al.*, 2012).

Second-order features are known to play an important role in identifying images. The studies aimed at studying the role of second-order visual mechanisms in the recognition of emotional stimuli (especially scenes) are of particular importance today. Scenes are complex visual stimuli. Compared to the mechanisms of visual perception of faces and objects, little attention has been devoted to studying the brain mechanisms underlying processing of scenes (Aftanas *et al.*, 2001; Codispoti *et al.*, 2007; Delplanque *et al.*, 2004; Mavratzakis *et al.*, 2016; Olofsson *et al.*, 2008; Pegna *et al.*, 2004). Due to the fact that the human visual system often recognizes the scenes as combinations of images that include various elements, the study of these mechanisms can help us to clarify our understanding of the process of visual perception *in vivo*.

At the same time, we should take into account the influence of individual characteristics on the processes of visual perception. These may include psychological and biological characteristics. The genetic factors in the individualization of visual perception, i.e. genes that can affect the mechanisms of visual perception of images (including emotional scenes) are the catechol-o-methyltransferase (*COMT*) gene, the brain derived neurotrophic factor (*BDNF*) gene, the serotonin receptor gene (*HTR2A*), etc. In the science periodicals numerous studies examine the associations between these genes and individual psychological characteristics, including emotional intelligence, aggression, anxiety, and neuroplasticity and describe neurochemical processes characteristic to carriers of various genotypes.

However, the influence of genes on the processes of visual perception, including the mechanisms for recognizing and evaluating (appraising) emotional visual stimuli (scenes) with the distinct second-order features are poorly described. This fact determined the topic of the present investigation. Let us now consider in more detail the functions of these genes.

***BDNF* - the brain derived neurotrophic factor gene**

BDNF is a key molecule involved in the plastic changes associated with learning and memory. The *BDNF* stimulates the growth of neurons, axons, and dendrites, the formation of synapses and other processes of neuroplasticity not only in early ontogenesis, but also in the brain of the adult organism (Antal *et al.*, 2010). Changes in *BDNF* expression in the brain structures involved in memory functions and perception processes (Miranda *et al.*, 2019) are associated with human normal and pathological aging, as well as with mental illness. Together with other neurotrophic factors, *BDNF* plays an important role in the processes of adaptation of brain neurons to various external impacts influences, as well as in their growth, differentiation, and survival (Popova *et al.*, 2017).

It is established that visual experience in the early postnatal period affects the maturation of the visual cortex. Furthermore, it was investigated the characteristics of maturation and plasticity of the visual cortex in mice with elevated level of *BDNF* (Huang *et al.*, 1999). Under experimental conditions of visual deprivation, the authors found that *BDNF* overexpression is sufficient for the development of normal activity of the visual cortex in the absence of visual experience. Meanwhile, a decrease in *BDNF* expression slows down the development of visual areas of the cerebral cortex under conditions of visual deprivation (Gianfranceschi *et al.*, 2003).

Carriers of the *BDNF* Val/Val genotype with higher cortical plasticity were characterized by a more thorough processing of visual images. This may be explained by a more detailed analysis of the components of visual images which is associated with a higher activation of occipital areas. There is also some evidence that carriers of *BDNF* Val/Val genotype with higher neural plasticity perform visual-motor adaptation tasks worse than carriers of Val/Met genotype (Ermakov *et al.*, 2017).

Compared to carriers of the Val/Val genotype, those with the Met allele of the *BDNF* gene demonstrate higher activation in amygdala and hippocampus when recognizing individuals expressing emotions (Vorobyeva *et al.*, 2019). These data indicate the contribution of the *BDNF* gene to the formation of brain mechanisms underlying anxiety, as well as its possible role in the recognition of emotional stimuli.

Andreatta *et al.* (2019) showed that carriers of the Met allele of the *BDNF* gene have a higher level of anxiety. Loewenstern *et al.*, (2019) confirmed this result, providing the following physiological data: the highly anxious carriers of the Met allele of the *BDNF* gene have stronger functional associations between the left amygdala and the right dorsolateral prefrontal cortex (anxiety phenotype).

According to (Schofield *et al.*, 2009), carriers of the Met/Met genotype of the *BDNF* gene had higher verbal recall errors and showed increased P300 latency when performing tasks in the oddball paradigm with corresponding alterations in hippocampal and lateral prefrontal activation, and a localized reduction in hippocampal gray matter. Thus, the Met allele affects the fronto-hippocampal systems involved in the selective processing of stimulus information and memory renewal in healthy individuals. Gajewski *et al.*, (2012) described the impact of the Met/Met genotype of the *BDNF* gene on fronto-striatal associations. Meanwhile, this genotype was associated with a decrease in the severity of the Stroop effect in elderly people, which was accompanied by an increase in the amplitude of the N450 component during task performance. Researchers concluded that carriers of the Met/Met genotype of the *BDNF* gene were more resistant to interference. In their earlier work (Gajewski *et al.*, 2010) also suggested that superior memory-based task-switching performance in elderly Met-allele carriers manifested itself in that N2 was increased while the P3 was decreased in Met-allele carriers. Beste *et al.*, (2010) associated the Met allele of the *BDNF* gene with fewer errors during task performance, as well as with a less time stability of information stored in iconic memory (Beste *et al.*, 2011).

COMT - the catechol-o-methyltransferase gene

This gene is associated with the dopamine system of the human brain. The enzyme catechol-O-methyltransferase regulates the transmission of impulses in the nervous system, and therefore can affect various mental processes (Serrano *et al.*, 2019). Carriers of the *COMT* Met allele differentiate emotions and understand facial expression significantly better than those with the Val allele (Gohier *et al.*, 2014b; Weiss *et al.*, 2014). The structural features of this gene are associated with the activity of working memory (Barnett *et al.*, 2011; Dumontheil *et al.*, 2011; Gosso *et al.*, 2008), multitasking ability (Rosa *et al.*, 2010), anxiety (Hashimoto *et al.*, 2007), extraversion (Reuter & Hennig, 2005) level of organization of regulatory (management) functions (Barnes *et al.*, 2011), impulsivity and novelty seeking (Golimbet *et al.*, 2006), and also the tendency to use psychoactive substances (Lovallo *et al.*, 2019).

Individuals with a high enzymatic activity of *COMT* (the Val/Val genotype of the *COMT* gene) are better able to deal with stressful situations, because excess dopamine activity is quickly neutralized. On the other hand, individuals with a low enzymatic activity of *COMT* (the Met/Met genotype of the *COMT* gene) are more capable to develop complex plans, calculate the probabilities of events and think about their consequences; they have better memory, the ability to synthesize new information, but in a calm environment, in the absence of stress (Stein *et al.*, 2006).

The data on the associations between the *COMT* gene genotypes and the brain correlates for facial expression recognition indicate that male carriers of the Met allele have higher values of latency of evoked potentials during perceiving faces; women with this genotype have a more pronounced arousal effect (Tamm *et al.*, 2016). Bender *et al.*, (2012) found that the *DAT1* and *COMT* genes affect the same specific time interval (early

contingent negative variation, CNV) associated with preparing for movement. According to (Gómez *et al.*, 2003), the generators of this component are located in the frontal cortex (anterior cingulate gyrus) and in the occipital-temporal visual cortex, which corresponds to the expression of the *COMT* gene. There is evidence for the linkage of the region of chromosome 22 containing the *COMT* gene with an integrated phenotype that includes visual-motor dysfunction (Alfimova & Golimbet, 2011).

Kondo *et al.* (2012) discovered the effect of the *COMT* gene on speech perception reflected in the induced brain activity, as well as the impact of *HTR2A* gene on the perception of inverted figures. Later, these authors examined associations between *COMT* genotypes and recognition accuracy, as well as associations between *HTR2A* genotypes and the response time for recognition (Kondo *et al.*, 2015).

HTR2A - the serotonin receptor gene

HTR2A has an inhibitory effect in the visual cortex. It is believed to be associated with episodic memory (Reynolds *et al.*, 2006) and emotional intelligence (Kosonogov *et al.*, 2019). Greater activation of the parieto-occipital areas of the brain during positive or negative judgment of stimuli by carriers of the dominant homozygous G/G genotype of the *HTR2A* gene may be explained their detailed assessment of stimulus images. Along with this, carriers of the recessive homozygous A/A genotype had similar activity in the same areas during positive emotional assessment of stimuli, which can be interpreted same way as G/G genotype (Alekseeva *et al.*, 2017; Ermakov *et al.*, 2017).

An analysis of the previous studies showed that knowledge of the role of genes in providing various mechanisms of perception is insufficient for creating a holistic picture. Certain aspects of this issue were investigated in a study conducted by (Nakagami *et al.*, 2013) in marmosets. This results suggest that the patterns of gene expression that are potentially associated with various stages of visual cognition are different in the neurons of each layer of the visual cortex. The regulation of each neuron of primary visual cortex in marmosets is subjected to various regulating impacts when the activity of the retina changes. It should be related to a highly differentiated laminar structure of marmoset visual systems, reflecting the functions of the activity-dependent gene expression. Consequently, *HTR2A* gene expression depends on the level of activation of the various retinal layers.

Based upon the foregoing, this study aims to examine the associations between *BDNF*, *COMT*, and *HTR2A* genotypes and individual characteristics of the perception of emotional visual stimuli (scenes) with distinct second-order features.

This study proposes the following research hypotheses

1) Amplitude, spatial, and temporal characteristics of the components of visual event-related potentials in response to emotional visual stimuli (scenes) with distinct second-order features are significantly different in carriers of different *BDNF*, *COMT*, and *HTR2A* genotypes.

2) Characteristics of attribution of emotional valences to visual stimuli (scenes) with distinct second-order features have statistically reliable difference in carriers of different *BDNF*, *COMT*, and *HTR2A* genotypes.

Methods

Ethical statement

The use of experimental subjects is in accordance with ethical guidelines as outlined in the Declaration of Helsinki. In addition, the design of the experiment, the methodological approach, the conditions of confidentiality and use of oral consent for the subjects was performed according to the Code of Ethics of Southern Federal University (SFU, Rostov-on-Don, Russia) and approved ethically by the Academic Council of the Academy of Psychology and Pedagogy of SFU, on 23 March, 2018. Oral consent for participating in research was approved since the study requires only a small amount information about the participant's genotype, gender and age and no other additional information. It should be noted that all data were encrypted and stored in the laboratory of the Department of psychophysiology and clinical psychology and only research personal had access to it. Before the start, each participant was informed about the goal of the research, procedure, experimental conditions, and safety of their personal data.

Participants and genotype analysis

This study involved 34 participants of both genders from 18 to 28 years (27 female), students of Southern Federal University. The study was conducted from April 27, 2018 to July 10, 2018 at the Laboratory of Psychophysiology and Experimental Psychology, Department of Psychophysiology and Clinical Psychology, Academy of Psychology and Education Sciences, Southern Federal University (Rostov-on-Don, Russia). The participants were recruited in person. Students received bonus points in their academic disciplines for their involvement in the study. All participants reported normal or corrected-to-normal vision and gave oral, informed consent before beginning experimentation. For genotype analysis buccal epithelial cells were collected from participants. Genotyping was carried out by the «Biologicheskie resheniya i tehnologii» (Moscow, Russia), where DNA was extracted from clinical material using the Proba-NK reagent kit («ООО ДНК-технологии», Russia). Thermocycler CFX96 «Touch» (Bio-Rad, USA) was used for real-time polymerase chain reaction (PCR).

For genetic analysis were used genomic DNA preparations obtained from biological samples using DNA extraction kits with the removal of PCR inhibitors and the presence of at least 100 genomic copies in 1 µl. During the genetic examination, the following DNA sections were analyzed:

– *COMT* catechol-O-methyltransferase gene (Genebank sequence AY341246, mutation 23753G> A, Val158Met, rs4680 code). Possible genotypes: Val/Val, Val/Met, Met/Met;

– *BDNF* brain neurotrophic factor gene (GenBank sequence NG_011794, mutation 68690G> A Val66Met, rs6265 code). Possible genotypes: Val/Val, Val/Met, Met/Met;

– *HTR2A* serotonin receptor gene (GenBank sequence, NG_013011, mutation 4692G> A, rs6311 (Tr2)). Possible genotypes: G/G, G/A, A/A.

The genotyping resulted in the following sample composition:

COMT gene: 9 participants (26.47 %) were carriers of Val/Val genotype, 20 (58.82%) – Val/Met and 5 (14.7 %) – Met/Met;

HTR2A gene: 11 participants (32.35 %) were carriers of A/A genotype, 11 (32.35 %) – A/G and 12 (35.29 %) – G/G;

BDNF gene: 23 participants (67.64 %) were carriers of Val/Val genotype and 11 (32.35%) Val/Met.

Preparing stimuli

For this research, 223 images were selected from a database used in previous experiments: 85 of them are conditionally negative, 75 are neutral and 63 are positive (Ermakov *et al.*, 2016; Ermakov *et al.*, 2017; Stoletniy *et al.*, 2020b; Vorobyeva *et al.*, 2016); stimuli are available as *Extended data* (Kovsh & Yavna, 2020). To obtain stimuli with corresponding characteristics, the computer model of the second-order visual mechanisms developed by (Babenko & Yavna, 2018) was applied. Figure 1 below demonstrates examples of original images and the results of their processing by the model. Stimuli images were generated from contrast modulations in the carrier frequency range from 4 to 32 cycle per image. Resolution of pictures is 1024x768 (slightly more 16°x12° of visual angle on the 100 cm distance). The average luminance of the generated images was equal to 110 of 256 greyscale (30 cd/m²). The background brightness was adjusted to the same level. All 223 selected images were processed and then organized in a stimulus sequence.

Procedure

Participants were seated in good lit room, facing a computer screen, at viewing distance of 100 cm. A grey background (30 cd/m²) was on the monitor all the time of trial, with and without stimuli. Stimulus image was presented in center of screen and its duration was 500 ms. The interstimuli interval was 500–1500 ms (Figure 2). Stimulus pictures were presented in random order regardless of their emotional valence. Participants were asked to examine the stimuli in terms of what emotions this images evokes in them. When evaluating the stimulus as negative, it was necessary to press the key 1 on the keyboard for negative assessment, 2 for neutral, 3 for positive. The next image appeared on the screen only after the subject evaluated the previous one and the interval between stimuli was completed. Furthermore, participants were instructed to blink only when stimulus ended.

Analysis of behavioral data and ERP recordings

The frequency of responses was analyzed using the REdaS Package for R, version 0.9.3., in order to calculate confidence intervals for average response rate with $\alpha = 0.05$ (Maier, 2015).

A Neurovisor-136 multi-channel EEG system («Medical Computer Systems», Moscow, Russia) was used to record the

Figure 1. Example of original images that was selected for processing are above; same images processed by a computer model of second-order mechanisms and made up of areas containing contrast modulations are below.

EEG from 128 electrodes mounted on elastic cap and referenced on the left and right ears. Electrodes were placed according to 10–5 system (Oostenveld & Praamstra, 2001). EEG signal was digitalized at 1000 Hz, and a bandpass filter of 0.5–50 Hz was applied.

The ERPs were processed using the **EEGLAB** version 4.11 – an interactive Matlab/Octave toolbox for processing electrophysiological data (Delorme & Makeig, 2004). Before averaging the ERPs, the recordings were filtered and the epochs with eye blinks and other artifact of non-brain origin were rejected. The ERPs were averaged 100 ms before the stimulus onset and 500 ms after it. Baseline was corrected based on 100 ms pre-stimulus period. ERPs were computed and grouped according to type of response that participants gave – negative, neutral and positive and their genotype. The ERPs grouped by type of emotional assessment were compared separately for *COMT*, *BDNF*, *HTR2A* samples (For example: *COMT* x Negative evaluation x Val/Val vs Val/ Met; Val/Val vs Met/Met; Val/Met vs Met/Met etc.). Comparisons were carried out using an unpaired Student's T-test with $p < 0.05$. ERPs and topography figures were conducted in **EEGLAB**. The results from all ERP stimuli are available as Underlying data (Stoletniy *et al.*, 2020a).

Results

Behavioral results

This analysis showed that there was no statistically reliable difference in the average response rate in participants with different *BDNF* gene genotypes regardless type of assessment of target images (Figure 3, upper line). Nevertheless, it should be noted that the ratio of the average number of choices of neutral responses is the reverse of that when choosing negative

and positive judgments; the individual participants with the Val/Val genotype chose the neutral response slightly more often than the participants with the Val/Met genotype.

Participants with different *COMT* genotypes chose negative assessments with an average frequency (about 32–33%). There were no significant differences in the frequency of negative responses in the groups. Nevertheless, the distribution of neutral and positive responses is of more interest (Figure 3, middle line). On the one hand, participants with the Val/Val and Val/Met genotype chose the positive assessment of stimuli significantly more often (19% and 13%, respectively) than carriers of Met/Met. On the other hand, the carriers of the Met/Met genotype were significantly often (18% and 13% compared to Val/Val and Val/Met groups) chose to evaluate the images as neutral. There were no significant differences between the average frequency of choosing the neutral and positive responses between the Val/Met and Val/Val groups.

Carriers of different *HTR2A* genotypes chose negative responses with different average frequency but no statistically reliable difference, because the confidence intervals do not intersect. Although the histogram has a stepwise character from a higher average frequency for carriers of the A/A genotype (39%) to lower frequency for carriers of the A/G (33%) and G/G (28%) genotype (Figure 3, bottom line). A more interesting situation has developed for the neutral and positive types of responses. Participants with the G/G genotype were significantly more likely (46%) to choose the neutral response when evaluating experimental stimuli than those with the A/A (25%) and A/G (29%) genotypes. On the contrary, the G/G group had chosen positive assessment less often (26%), than A/A (37%) and A/G

Figure 2. Example of trial sequence with target stimuli and ISI between them.

Figure 3. Bar graphs with confidence intervals ($\alpha = 0.05$) for the average frequency of assessment responses for stimuli for participants with different genotypes of *BDNF*, *COMT* and *HTR2A* genes. MM- Met/Met genotype, VM – Val/Met, VV- Val/Val for *COMT* and *BDNF* genes; AA – A/A, AG – A/G, GG – G/G for *HTR2A* gene.

(37%) groups. There was no statistically reliable difference between the average frequency of choosing the neutral and positive responses between the A/A and A/G groups.

ERP data analyses

BDNF. The comparison of event-related potentials when choosing the negative assessment in the groups of carriers of Val/Met and Val/Val genotypes showed significant differences in the amplitude of the event-related response ($p < 0.003$, $t = -3.5$)

in the time range of 150–230 ms (Figure 4a). As can be clearly seen in the figure, the amplitude of the P2 component of the ERP recorded for negative response in participants with the Val/Val genotype is significantly higher than that of the Val/Met group. When choosing the neutral assessment statistically significant differences were found in latency of 172–227 ms (Figure 4b). The ERP amplitude in the group of carriers of the Val/Val genotype is significantly higher ($p < 0.02$, $t = -1.22$) than that of the Val/Met group. Choose of positive response to the stimuli

Figure 4. ERP for the groups with Val/Met and Val/Val *BDNF* genotypes in Oz electrode when choosing the negative (a), neutral (b) or positive (c) assessment of stimuli. The gray bar indicates the latency with statistically significant differences ($p < 0.05$).

elicited an increase in amplitude of ERP peak in the latency of 133–230 ms. ERP peak for the Val/Val group was significantly higher ($p < 0.029$, $t = -2.36$) than that of the Val/Met group (Figure 4c). Table 1 presents the values of the ERPs amplitudes in Oz electrode at a latency of 200 ms for the *BDNF* group.

The topography of the potentials distribution shows that the choice of the negative response caused activation in the occipital regions of the cortex. Moreover, it was higher in the group of carriers of the Val/Val genotype of the *BDNF* gene (Figure 5a). The choice of the neutral assessment caused activation in the occipital regions of the cortex to a greater extent in the group of carriers of the Val/Val genotype (Figure 5b). Nevertheless, activity in the anterior and central areas of the cerebral cortex is somewhat greater in the group of participants with the Val/Met genotype of the *BDNF* gene. Selection of the positive assessment caused an increase in the amplitude of positive peaks in the region of 140–230 ms in the occipital regions of the cortex, to a greater extent in carriers of the Val/Val genotype of the *BDNF* gene, as in both previous cases (Figure 5c).

COMT. The comparison of ERPs in the groups of participants with the Val/Met and Val/Val genotypes did not show significant differences regardless of assessment type: for negative, $p < 0.94$, $t = -0.06$; for neutral, $p < 0.59$, $t = -1.7$; for positive, $p < 0.95$, $t = -0.10$ (Figure 6a–c, solid and intermittent waves on the figures). On the contrary, amplitude of the event-related potentials in participants with the Met/Met genotype is significantly lower compared to Val/Val and Val/Met groups during every type of assessment (Figure 6, a, b, c, dotted wave). For negative evaluation this differences were observed in latency to the 110 to 175 ms (Val/Met - $p < 0.03$, $t = -2.33$; Val/Val - $p < 0.03$, $t = 0.6$), for neutral in 120 to 170 ms (Val/Met - $p < 0.006$, $t = -3.10$, Val/Val - $p < 0.03$, $t = 2.19$), for positive -135 to 155 ms (Val/Met - $p < 0.02$, $t = -1.39$, Val/Val - $p < 0.03$, $t = -2.39$). It should be noted that the

amplitude of the event-related potential for Met/Met is higher when participants assessed stimuli as the neutral and positive, then negative ones. Table 1 presents the values of the ERPs amplitudes in Oz electrode at a latency of 150 ms for the *COMT* group.

Topography of potentials clearly shows a decrease in activity of occipital regions in the Met/Met group in latency of 150 ms comparing to Val/Met and Val/Val groups. On the contrary Val/Met and Val/Val group showed increase in activity also in the occipital regions of the brain (Figure 7a–c).

HTR2A. Comparing the ERPs of A/G and G/G genotype groups showed no statistical difference between them, regardless of assessment type – negative ($p < 0.17$, $t = 1.41$), neutral ($p < 0.56$, $t = -0.59$) or positive ($p < 0.84$, $t = -0.19$). At the same time, chose a negative response type demonstrated that the amplitude of ERP in carriers of the A/A genotype was significantly different from such of the A/G genotype ($p < 0.03$, $t = 2.29$) and G / G ($p < 0.04$, $t = 3.12$) in the range of 117–133 ms from the onset of stimulus (Figure 8a). Choosing neutral response by carriers of A/A genotype reflected in significant decrease of ERP component's amplitude in 350–370 ms latency compared to A/G ($p < 0.02$, $t = -2.47$) and G/G ($p < 0.03$, $t = -2.25$) groups (Figure 8b). Similar to ERP comparison for negative assessment, evaluating stimuli as positive by carriers A/A genotype showed significant increase of ERP amplitude in latency 105 to 124 ms compared to such in A/G ($p < 0.01$, $t = 2.72$) and G/G ($p < 0.03$, $t = 2.32$) genotype carriers (Figure 8c). Table 1 presents the values of the ERPs amplitudes in Oz, Po7 and Poz electrodes at a latency of 120 and 360 ms for the *HTR2A* group.

The topography of the distribution of potentials shows a high positivity when choosing negative assessment mainly in the occipital regions of the A/A group and a tendency to decrease of it in same regions in the group of carriers of the A/G genotype, and to a greater extent – in carriers of the G/G genotype

Table 1. Examples of amplitudes for ERP peaks in latency and locations where statistically significant differences were found.

Gene and genotype	Type of response/location/latency/Place amplitude		
BDNF	Negative (Oz, 200 ms)	Neutral (Oz, 200 ms)	Positive (Oz, 200 ms)
Val/Met	3.71	4.49	4.05
Val/Val	6.68	7.41	6.56
COMT	Negative (Oz, 150 ms)	Neutral (Oz, 150 ms)	Positive (Oz, 150 ms)
Met/Met	-0.54	0.69	0.72
Val/Met	2	3.78	3.76
Val/Val	2.9	3.06	3.57
HTR2A	Negative (Oz, 120 ms)	Neutral (Po7, 360 ms)	Positive (Poz, 120 ms)
A/A	6.07	0.53	6.20
A/G	1.87	3.24	4.24
G/G	3.33	2.75	3.72

Figure 5. Topography of the distribution of potentials at a latency of 200 ms (where statistically significant differences were found) from onset of stimuli when choosing negative (a), neutral (b) or positive (c) assessment for the Val/Met and Val/Val *BDNF* genotypes.

(Figure 9a). In the neutral response situation ERP amplitude distribution in carriers of the A/A genotype is somewhat homogeneous over the entire surface of the scalp. However, in carriers of the A/G and G/G genotypes it is much greater in the occipital and parietal regions (Figure 9b). When choosing the positive response, high-amplitude ERPs are localized in the occipital regions. Moreover, the activity in the A/A group is most higher, to a lesser extent it is expressed in the A/G group, and even lower in G/G groups (Figure 9c).

Discussion

As shown in the *Results* section, the *BDNF* Val/Val genotype is associated with a predominance of neutral assessment of visual stimuli processed by second-order filters. Neutral, positive, and negative judgments of visual stimuli are associated with a significantly higher positivity of the P2 component in the occipital electrodes, which may be explained by the fact that compared to the carriers of *BDNF* Val/Met genotype the carriers of the *BDNF* Val/Val genotype consumed large brain resources for recognition and differentiation of stimuli, experiencing difficulties in the implementation of these processes. Moreover, brain

activity in the anterior and central areas is more pronounced in carriers of the Val/Met genotype. We obtained similar results in previous series of the experiment (during recognition of unprocessed visual stimuli), which may indicate that the Met allele of the *BDNF* gene is associated with more efficient processes of recognition of emotional scenes (Ermakov *et al.*, 2017). This feature can be explained by a more intense activation of the structures of the limbic system (Vorobyeva *et al.*, 2019) and stronger functional cortico-limbic bonds (Loewenstern *et al.*, 2019), activated during recognition of facial expression in carriers of the Met allele of the *BDNF* gene.

According to our results, when judging the stimulus as negative, neutral, or positive negativity was reliably expressed in 110–175 ms (i.e., there is a higher, more negative amplitude of the N170 component) in the occipital electrodes in carriers of the *COMT* Met/Met genotype.

This aspect may be related to the fact that, when evaluating scenes with distinct second-order features, the carriers of the *COMT* Met/Met genotype primarily pay attention to the facial

Figure 6. ERP for the groups with Val/Met, Val/Val and Met/Met *COMT* genotypes in Oz electrode when choosing the negative (a), neutral (b) or positive (c) assessment of stimuli. The gray bar indicates the latency with statistically significant differences ($p < 0.05$). Significant differences between ERPs in Val/Val and Val/Met groups were not found.

expression of individuals depicted in the stimulus pictures and assess the emotional valence of the stimulus based on these data (Eimer & Holmes, 2007). However, this process consumes more brain resources to recognize faces emotional expression.

According to a number of studies, carriers of the *COMT* Met/Met genotype have higher indices of emotional intelligence (Kosonogov *et al.*, 2019), more successfully differentiate and express emotions (Gohier *et al.*, 2014a). Carriers of the *COMT*

Figure 7. Topography of the distribution of potentials at a latency of 150 ms (where statistically significant differences were found) from onset of stimuli when choosing negative (a), neutral (b) or positive (c) assessment for the Met/Met, Val/Met and Val/Val *COMT* genotypes.

Met/Met genotype more decently respond to positive stimuli. The Val/Val genotype is associated with less intense feelings in negative experience, i.e. their level of life satisfaction is less dependent on external events (Kovalenko & Pavlenko, 2009; Shield *et al.*, 2004).

The *HTR2A* G/G genotype is associated with a significantly more frequent evaluation of stimuli with distinct second-order features as neutral ones, as well as with a significantly rarer assessed of stimuli as positive ones. The A/A genotype is associated with a significantly higher amplitude of the P1 peak, recorded mainly in the occipital regions of the brain when evaluating visual stimuli processed by second-order filters as positive or negative ones; with a significantly lower wave amplitude in the range of 350–370 ms when assessed as

emotionally neutral. These results may indicate that carriers of A/A genotype consume more brain resources at the stage of distinguishing of a significant stimulus among insignificant ones, experiencing difficulties in the implementation of this process (difficulties in pre-attentive processing; component P1 is associated with selectivity of attention), and less resources are consumed during categorization and conscious evaluation of the emotional content of stimuli (Kovalenko & Pavlenko, 2009; Polich, 2012).

Conclusions

The analysis of the electrical activity of the brain in carriers of various genotypes of the *BDNF*, *COMT*, and *HTR2A* genes when choosing different types of responses in attributing emotional valences to visual scenes processed by the filters

Figure 8. ERP for groups with different *HTR2A* genotypes in Oz, Po7 and Poz electrodes when choosing negative (a), neutral (b) or positive (c) assessment respectively. The gray bar indicates the latency with statistically significant differences ($p < 0.05$). Significant differences between ERPs in A/G and G/G groups were not found.

Figure 9. Topography of the distribution of potentials at a latency of 120 ms from onset of stimuli (where statistically significant differences were found) when choosing negative (**a**) or positive (**c**) and 360 ms when choosing neutral (**b**) assessment for the A/A, A/G and G/G *HTR2A* genotypes.

with the distinct second-order features enabled us to draw the following conclusions.

BDNF

1) In carriers of the Val/Val genotype the amplitude of the P2 component of visual event-related potentials in the occipital regions of the brain is higher than in carriers of the *BDNF* Val/Met genotype, regardless of the type of response chosen when evaluating the presented images.

2) The highest ERP amplitude of the three possible assessments (positive, negative, neutral) was found in the response recorded in the neutral evaluation of the presented stimuli; this fact is valid for carriers of the *BDNF* Val/Val and Val/Met genotypes.

3) Regardless of the type of stimuli, the participants chose responses of different modalities with approximately the same frequency.

COMT

1) In the group of participants with the *COMT* Met/Met genotype for all the three types of responses (regardless the stimuli images) the induced brain activity is characterized by a significant increase in negativity in peak amplitude latency from 120 to 170 ms and occurs mainly in the occipital cortex brain.

2) When carriers of Met/Met assessed the stimuli as negative the amplitude of this early ERP component is showed increasing negativity, compared with that when choosing neutral or positive responses.

3) Met/Met genotype carriers statistically reliably chose neutral assessment more often and positive less often than carriers of other two genotypes.

HTR2A

1) There were no statistically significant differences between the ERP waves in carriers of the *HTR2A* A/G and G/G genotypes, regardless of the choice of the emotional valences of responses. On the contrary, A/A group had statistically reliable differences in ERPs peaks compared to A/G and G/G genotypes carriers.

2) When choosing negative and positive assessment, carriers of A/A genotype had statistically reliable differences in early latency peak that had large amplitude, compared to A/G and G/G genotypes carriers. Contrariwise, in neutral assessment situation, a statistically reliable differences in ERPs shifted to later positive peak (around 360 ms) that had an increasing negativity in participants with A/A genotype.

3) The localization of activity also has differences in carriers of different *HTR2A* genotypes. When choosing negative and positive responses, the topography of significant high-amplitude components of the ERP shows their localization in the occipital regions; with a late latent significant ERP when choosing a neutral type of responses, increased activity also affects the parietal areas (which is more reliable to carriers of the A/G and G/G genotypes compared to carriers of the A/A genotype).

4) G/G genotype carriers were significantly more often chose neutral response and less often positive response for stimuli than carriers of other two genotypes.

In this study, associations between the *BDNF*, *COMT*, and *HTR2A* genotypes and individual characteristics of the perception of emotional visual stimuli with distinct second-order features were investigated. The findings of the study confirmed both hypotheses of the research. Furthermore, the results lead to conclusion that the images preserving second-order features, where all the homogeneous areas are removed, contain all the necessary information for their successful recognition. This may be explained

by the work of autonomous mechanisms operating at a pre-attentive stage of visual processing (Babenko & Yavna, 2018). At the same time, various genotypes are associated with varying degrees of success of the pre-attentive and conscious stages of processing emotional visual stimuli (scenes), which confirms the hypothesis that there are genetic factors that individualize the mechanisms of visual perception.

Data availability

Underlying data

Open Science Framework: EEGLAB datasets for study of event-related potentials during categorization of emotionally-charged and neutral images with distinct second-order features in carriers of polymorphisms of the *COMT*, *HTR2A*, *BDNF* genes. <https://doi.org/10.17605/OSF.IO/PDHGZ> (Stoletniy *et al.*, 2020a).

This project contains the follow underlying data:

- 1_Negative estimation (ERP datasets recorded when participant chose negative assessment of stimuli).
- 2_Neutral estimation (ERP datasets recorded when participant chose neutral assessment of stimuli).
- 3_Positive estimation (ERP datasets recorded when participant chose positive assessment of stimuli).
- Data Characteristics.xlsx (detailed description of datasets files).
- Data Description.docx (detailed description of experiment condition and datasets).

Extended data

Open Science Framework: Stimuli database for studying emotional assessment of emotionally-charged images with distinct second-order features. <https://doi.org/10.17605/OSF.IO/WY2VF> (Kovsh & Yavna, 2020).

This project contains all visual stimuli provided for this study, alongside a data description list of the image features.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Talis Bachmann

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1. The language of this paper is extremely poor both in terms of grammar and idiomatic aspects. This makes it very difficult to smoothly read the text and get precisely to what the authors want to say. In many places sentences do not make sense or are impossible to understand unambiguously: e.g., p 4 left column, middle ("Carriers of the COMT Met allele..."), p 4 right column, middle ("An analysis of the previous..."), p 6, left column, middle ("The ERPs were averaged 100 ms before..."), etc.
2. In many places there are no references to the sources of statements about factual knowledge from earlier research (e.g., p 3 bottom left, 3rd para from bottom right).
3. The buildup from Introduction to hypotheses is poor and unfocused. Why study specifically these genes in light of the set tasks and hypotheses? Theoretical introduction is eclectic and does not clearly lead to specific hypotheses. It is never mentioned that the study is essentially exploratory.
4. The description of the method is cryptic in several places and terms used are too often vague, unspecified and different from what is currently used in the worldwide publications on the topic. Page 5, middle: "... stimuli with corresponding characteristics..." -- what does this precisely mean? Few lines further down: "Resolution of pictures is 1024x768 (slightly more 16degx12deg of visual angle..." -- display resolution is lumped with visual angle of the screen. Further down, "The next image appeared on the screen only after the subject evaluated the previous one and the interval between stimuli was completed" contradicts the earlier description of the trial timing. 'Second order mechanisms' are used instead of, e.g., spatially filtered original images. Page 6, Results: first sentence of the Behavioral results -- 'average response rate' is not sufficiently clear what is meant by this. The design is difficult to understand because on the one hand there are pictures with different emotional connotations, on the other hand there are different response options. How these are interrelated is difficult to comprehend.

5. Some aspects of the method are questionable. For example, the frequency of presentation of stimuli with different affective categories is unequal, possibly leading to artefacts. Value and arousal dimensions of pictures are not controlled and counterbalanced or cross-varied. The time intervals between successive stimulation presentations may be too short. (For instance, readiness potentials, CNVs and evoked potentials may be mutually cancelled or noised. There is no clear P300 visible, which is suspect for data analysis.) The conclusion "Regardless of the type of stimuli..." (p 14, 3)) hints at the possibility that there is something wrong in the design.
6. Conclusions in the Discussion and at the end can not be derived from the carried-out study as if they are firmly supported.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Experimental psychology, psychophysiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 16 December 2020

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Elena Samoylenko

Institute of Psychology, Russian Academy of Sciences, Moscow, Russian Federation

1. Why were COMT, BDNF and HTR2A genes selected for the study, although the article deals with topic of visual perception?
2. Why was the analysis approach with intragroup comparison for one gene chosen, and not comparison for combinations of all genes genotypes?
3. EEG and ERP were recorded in 128 scalp electrodes. You did not indicate if you applied correction for multiple comparisons.
4. Sample of participants is sufficient for ERP study, but small enough for genetic research. Please add "Limitation" section in the article and describe confines of research due to relatively small sample size.
5. Please unify the designation of the ERP components - either P1 or P100 type of writing.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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