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Aggression and 5HTT polymorphism in females: Study of synchronized swimming and control groups

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ABSTRACT

Aggression is a heterogeneous heritable psychological trait, also influenced by environmental factors. Previous studies, mostly conducted on male population, have found some associations of the aggression with the polymorphisms of genes, regulating the activity of serotonin (5-HT) in the brain. However, psychological as well as biochemical manifestations of the aggression are different in males and females. Our study aimed to investigate the association of 5-HTT gene polymorphism with different facets of aggression (BDHI) in females. Two groups: the synchronized swimming and non-athlete control, — were examined to study the possible modulation effect of sport on the association between 5-HTT gene polymorphism and aggression. It was found that in both groups the low-active 5-HTT polymorphism (SS) was associated with increased scores on Indirect Hostility scale and decreased scores on Negativism scale, compared to LL genotype. No interaction effect between sport and 5-HTT polymorphism was found. The higher percentage of LL-carriers and lower of LS-carriers in the synchronized swimming group compared to the control one was observed. This may be the sign of the importance of LL polymorphism of 5-HTT gene, previously associated with higher resistance to stress factors, for being an athlete, although this result has to be taken cautiously keeping in mind the stratification problem. Synchronized swimmers had lower scores on Assault, Negativism, Irritability and Verbal Hostility compared to age-matched control girls (in general and for each 5-HTT genotype separately), suggesting that they may have more matured emotional system (older control group has also lower scores on these scales).

1. Introduction

Aggression usually refers to behavior that is intended to harm or hurt others. Eight facets of aggression can be estimated with the use of Buss–Durkee Hostility Inventory (BDHI) in humans: Assault (physical violence against others); Indirect Aggression (devious hostility like gossip); Irritability (quick temper, ready to explode at slight provocation); Negativism (usually oppositional behavior against authority, refusing to cooperate); Verbal Aggression (express negative feelings in content and style, e.g., shouting); Resentment (jealousy, anger at the world over mistreatment); Suspicion (projection of hostility into others); Guilt (reflecting the degree of guilt feelings reported by the subject). Some researchers unit these facets in higher order factors, but the results are not congruent with respect to facet loadings.

It is likely, that aggression is a result of biological and environmental factors interactions. Previous twin studies have indicated that aggression is a highly heritable trait. The heritability of aggression has been shown to be between 50% and 75% depending on age and gender of the studied population (Bartels et al., 2003; Eley et al., 1999; Hudziak et al., 2003; van Beijsterveldt et al., 2003). Genes underlying aggression can be found among genes which control different neurotransmitter systems.

One of the most researched neurotransmitter systems with regard to the aggression is serotonin system. It was shown that Central Nervous System (CNS) serotonergic activity correlates inversely with human aggressive behavior (Giammanco et al., 2005). PET study revealed that serotonin transporter (5-HTT) availability was significantly reduced in the anterior cingulate cortex of individuals with impulsive aggression compared with healthy subjects (Frankle et al., 2005). The 5-HTT is responsible for the reuptake of serotonin (5-HT) from the synaptic cleft and determines the magnitude and duration of postsynaptic receptor-mediated signaling (Lesch and Merschdorf, 2000).

The polymorphism in promoter region of 5-HTT gene (SLC6A4) has demonstrated functional significance in coding high (L-allele) and low (S-allele) transporter production. According to classical studies of

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Lesch (Lesch and Merschdorf, 2000) S-allele of 5-HTT is associated with the increased scores of neuroticism (negative emotionality), anxiety, hostility and depression. There are other evidences that polymorphism of gene 5-HTT promoter region is connected with the aggressive behavior (Beitchman et al., 2006; Gerra et al., 2005; Lesch and Merschdorf, 2000; Popova, 2006). It was shown that SS genotype is more frequent among aggressive drug experimenters than among abstinent students (Gerra et al., 2005) and among aggressive children (Beitchman et al., 2006). Aggressiveness (total BDHI) and Novelty Seeking (TQI) was higher for SS compared to LL genotypes (Gerra et al., 2005). Recent study (Pezawas et al., 2005) reported that S-allele carriers had reduced grey matter volume in perigenual cingulate and amygdala, and, moreover, decreased the functional interaction between these regions during processing of fearful stimuli.

Several lines of evidence demonstrate gender-related difference in the 5-HT-system functioning in human and animals (cf. Lesch and Merschdorf 2000). The mean rate of 5-HT synthesis in normal males was found to be 52% higher than in normal females (Nishizawa et al., 1997). Common belief is that generally females are less aggressive than males (Coie and Dodge, 1998). However, some researchers have suggested that women are not necessarily less aggressive, but that they tend to show their aggression in less overt, less physical ways (Bjorkqvist et al., 1994). It is noteworthy, that most genetic association study on aggression did not separate males and females in the analysis and involved mostly males. The genetic association studies on Neuroticism, involving large samples groups, are not conclusive in respect of the sex effect. Recent study reports the significant association of mean scores of Neuroticism with S-allele, but only for male population (Du et al., 2000). Moreover, the tendency in female group was in the opposite direction (Du et al., 2000; Gelernter et al., 1998), although other studies did not found the significant interaction effect between sex and 5-HTT gene polymorphism (Munafo et al., 2004; Willis-Owen et al., 2005). Studies of Middeldorp (Middeldorp et al., 2008, 2006) also suggest that men and women are alike in their symptom profiles for major depression and genes for depression are probably expressed in the same way in the two sexes.

Nonetheless, it is important to examine males and females separately. Our studies investigated the association between different facets of aggression with 5-HTT polymorphism in females.

Our previous study found the association of 5-HTT polymorphism with aggression in synchronized swimmers (Maliuchenko et al., 2007). It was found that carriers of SS genotype had higher scores on Indirect Hostility and lower on Negativism and Irritability scales compared to carries of other 5-HTT polymorphisms. The new complex scale of "covert aggression", characterized by dominance of indirectly or latterly expressed aggression signs, and lacking the direct aggression signs, such as disagreement and irritability, was suggested. It is calculated as the sum of normalized values of Negativism and Irritability with negative sign and Indirect Hostility with positive one. This "covert aggression" scale showed high association with 5-HTT polymorphism in synchronized swimming females.

Current study aims in investigating the differences in BDHI aggression scores between the synchronized swimmers and the control group of females, who is not involved in any professional sport. The association between the polymorphism of 5-HTT gene and the aggression was also examined on this expanded group. The possible modulation effect of sport on this association was also a point of interest. The distribution of 5-HTT gene polymorphism in the two studied groups was examined to shed the light on the possible genetic predisposition to the sport (synchronized swimming).

2. Methods

2.1. Subjects

A total of 166 healthy Caucasian female volunteers (10–26 years old) participated in the study. Sixty two of them were a qualified (from First-class athletes to Master of Sport)[1] synchronized swimmers (10–18 years old), recruited from the Moscow Professional sport club for synchronized swimming, uniting promising athletes from all over Moscow. The other 64 volunteers formed an age-match control group (10–18 years old), which were recruited from Moscow schools. There were also 40 volunteers (20–26 years old) recruited from the students, mostly of biological department.

2.2. Study protocol

The volunteers were asked to fill Buss–Durkee Hostility Inventory (BDHI), adapted by Osnitsky (Osnitsky, 1994) to Russian population and the age group (10–26 years old). The questioner contained 75 items unites in 8 scales: Assault, Indirect Hostility, Irritability, Negativism, Suspicion, Resentment, Verbal Hostility and Guilt. The subjects had to make the yes/no judgment if the item corresponds to them or not.

The sportgirls filled the questioner in the middle of the day between the training sessions. Their blood was collected as a part of regular health control procedure. For the age-matched control girls the experimental procedure was a part of a lesson, introducing the biological department. The schoolgirls filled the questionnaire and gave the saliva sample. The older control group (students) came to the experimenters' room to fill the questionnaire (one room) and to give the blood sample (another room). The filling of the questionnaires were always supervised by the investigators. All participants or their parents gave informed concern after the nature of the study was explained to them. The study was approved by the local Institutional Ethical committee.

2.3. Genotyping

For 5-HTTLPR genotyping, genomic DNA was extracted from venous blood and saliva samples according to standard procedures. Primers 5′-ATGCCAGCACCTAACCCCTAATGT-3′ and 5′-GACCG-CAAGGTGGGCGGGA-3′ were used to amplify a product that was 256 base pair (bp) product for the 14-repeat (s) allele and a 300 bp product for the 16-repeat (l) allele. Amplification reactions were performed in a total volume of 25 μL, containing approximately 100 ng of genomic template, 10 pmol of each primer, 0.2 mmol/L of each deoxynucleoside triphosphate (dNTP), 2.5 mmol/L of $MgCl_2$, 16 mmol/L $(NH_4)_2SO_4$, 0.125 mg/ml BSA, 8% glycerine, 0,001% xylencyanol and 2.5 unit of Taq polymerase. The polymerase chain reaction (PCR) cycling conditions consisted of an initial denaturation for 1 min at 94 °C, followed by 35 cycles of 94 °C for 30 s, 65 °C for 30 s, and 72 °C for 30 s. Polymerase chain reaction products were separated on a 3% agarose gel and visualized by ethidium bromide staining.

The polymerase chain reaction (PCR) based restriction fragment length polymorphism assay and real-time PCR were used in parallel. Analyses were carried out by different independent people. Fifty two DNA samples were run in duplicate. Only one mismatch was detected — that sample was excluded.

2.4. Statistical analysis

The Analysis of Covariance (ANCOVAs) with the genotype and sport status as the independent categorical factors consisting respectively of 3 levels (LL, LS, SS) and 2 levels (synchronized swimmer, control group) and age as controlling predictor variant for the complex scale of "covert aggression" and each primary scale of aggression separately were used. The "covert aggression" scores were calculated as the sum of normalized values of Negativism and

[1] According to Unified Sports Classification System of the Russian Federation the following hierarchy exists: First-class athlete equates to regional champion Candidate for Master of Sport, which equates to nationally ranked player, Master of Sports, equates to national champion.